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of LIVERPOOL

Highly Enantioselective Synthesis of Amines by Asymmetric Hydrogenation

Thesis submitted in accordance with the requirements of the
University of Liverpool for the degree of
Doctor in Philosophy

By

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To all of my family and friends

谨以此作献给我的妻子女儿,家庭成员和所有关心支持良师益友!

Preface

This thesis is based on research work developed at the Liverpool Centre for Materials and Catalysis, Department of chemistry, The University of Liverpool. The common denominator was found to be the mutual interest in chiral reduction of C=N double bonds by sustainable, easily accessible and most eco-friendly manner both in academic and industrial application.

Parts of this thesis have appeared in the following articles that were co-written by the author:

- "Metal-Bronsted Acid Cooperative Catalysis for Asymmetric Reductive Amination" **Li, C. Q.**; Villa-Marcos, B.; Xiao, J. L.* *J. Am. Chem. Soc.* **2009**, *131*, 6967. (highlighted by SYNFACT and *Angew. Chem. Int. Ed.* **2009**, 7124.)

- "pH-Regulated Asymmetric Transfer Hydrogenation of Quinolines in Water" Wang, C.; **Li, C. Q.**; Wu, X.; Xiao, J. L.* *Angew. Chem. Int.Ed. Engl.* **2009**, 6524. (highlighted by SYNFACT)

- "Chiral Counteranion-aided Asymmetric Hydrogenation of Acyclic Imines" **Li, C. Q.**; Wang, C.; Villa-Marcos, B.; Xiao, J. L.* *J. Am. Chem. Soc.* **2008**, *130*, 14450. (highlighted by SYNFACT)

- "Asymmetric Hydrogenation of Cyclic Imines with an Ionic Cp*Rh(III) Catalyst" **Li, C. Q.**; Xiao, J. L.* *J. Am. Chem. Soc.* **2008**, *130*, 13208 (highlighted by SYNFACT).

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CONTENTS

Chapter 1-Introduction

1	General methods for amine synthesis	1
1.1	Asymmetric catalysis and asymmetric hydrogenation	1
1.2	Importance of chiral amines	3
1.3	Methods of chiral amine synthesis	5
2	Asymmetric hydrogenation of imines and imino esters	10
2.1	Introduction	10
2.2	Transition metal-catalyzed asymmetric hydrogenation	13
2.2.1	Asymmetric hydrogenation of imines with Ti complexes	13
2.2.2	Asymmetric hydrogenation of acyclic imines with Rh catalysts	15
2.2.3	Asymmetric hydrogenation of acyclic imines with Ir catalysts	22
2.2.4	Asymmetric hydrogenation of acyclic imines with Ru catalysts	34
2.2.5	Asymmetric hydrogenation of acyclic imines with Au catalysts	36
2.2.6	Asymmetric hydrogenation of cyclic imines	37
2.2.7	Asymmetric hydrogenation of C=N-X substrates	41
2.2.8	Asymmetric hydrogenation of imino esters	45
2.2.9	Asymmetric transfer hydrogenation of imines with metal catalysts	47
2.3	Metal-free catalytic asymmetric hydrogenation	50
2.4	Organocatalytic asymmetric transfer hydrogenation	52
2.4.1	Reduction of imines	52
2.4.2	Reduction of imino esters	54
2.5	Mechanistic aspects of asymmetric hydrogenation	56
3	Direct asymmetric reductive amination	59

3.1 Introduction 59

3.2 Transition metal-catalyzed DARA 62

3.3 Organocatalytic asymmetric reductive amination 69

4 Conclusion 71

5 References 73

Chapter 2-Asymmetric Hydrogenation of Cyclic Imines with an Ionic Cp*Rh(III)-TsDPEN Catalyst

1 Introduction 83

2 Results and discussion 86

2.1 Additive effect 86

2.2 Hydrogen pressure effect 93

2.3 Asymmetric hydrogenation of cyclic imines **4** 94

2.4 Asymmetric hydrogenation of cyclic imines **6** 99

2.5 Asymmetric hydrogenation of acyclic imines 102

3 Conclusion 104

4 Experimental section 104

5 References 119

6 ^{1}H NMR Spectra 124

Chapter 3-Chiral Counter Anion-Aided Asymmetric Hydrogenation of Acyclic Imines

1 Introduction 126

2 Results and discussion 127

2.1 Chiral diamine-ligated Ir(III) and chiral anion system 127

2.2 Chiral diamine-ligated Ir(III) and achiral anion system 134

2.3 Achiral organometallic complex and chiral anion system 136

3 Mechanistic aspects 139

4 Conclusion 141

5 Experimental section 142

6 References 170

7 ^{1}H NMR Spectra 174

Chapter 4-Metal Brønsted Acid Cooperative Catalysis for Asymmetric Reductive Amination

1 Introduction 176

2 Results and discussion 177

2.1 Reductive amination of ketones 177

2.2 Reductive amination of keto esters 190

3 Conclusion 193

4 Experimental section 194

5 References 219

6 ^{1}H NMR Spectra 222

Chapter 1. Introduction

1 General Methods for Amine Synthesis

Asymmetric catalysis is one of the most important approaches to introduce one or more new and desired chiral elements to a prochiral substrate.[1-6] It is very important in the field of synthesis of enantiomerically pure compounds because different enantiomers or diastereomers of a molecule often have completely different biological activities.[2-4] As an important element of drugs, most of chiral amines were generated by efficient catalytic enantioselective reactions.[2,5,6] Synthesis of chiral amines by asymmetric catalysis will provide solution to industry in particular and society in general. In this chapter, a brief introduction of the concept of asymmetric catalysis, asymmetric hydrogenation, importance of chiral amines, and general synthetic routes will be given. An overview of the state of art enantioselective hydrogenation to chiral amines will also be presented.

1.1 Asymmetric Catalysis and Asymmetric Hydrogenation

Synthesis of enantiomerically pure compounds is one of the big challenges in organic chemistry and a major goal in the industrial synthesis of pharmaceuticals, agrochemicals, and fine chemicals.[2-4,6] In the past few decades, numerous chiral compounds have been obtained based on three strategies: chemical transformation of an enantiomerically enriched precursor, resolving a racemic mixture of the two enantiomers, or asymmetric catalysis.[2,4] The former two approaches suffer from potentially severe drawbacks, requiring stoichiometric amounts of a suitable precursor or affording only up to 50% yield of the desired enantiomer. Asymmetric catalysis, in

which each molecule of chiral catalyst, by virtue of being continually regenerated, can yield many molecules of chiral product, has significant potential advantages over the two older approaches. Bredig, the pioneer of investigation of enantioselective catalysis in 1908, reported the first preparation of enantiomerically enriched mandelonitrile from benzaldehyde and HCN by using an alkaloid as a chiral catalyst.[7] A major contribution of asymmetric catalysis has been achieved by three famous chemists, William Knowles, Ryoji Noyori and Barry Sharpless, who work on asymmetric hydrogenation and asymmetric oxidation. In recognition of their achievements, they shared the 2001 Nobel Prize in chemistry. Partly due to their effort, numerous efficient enantioselective catalytic systems have been developed for synthesis of chiral products in the past few decades.[2-4,8,9]

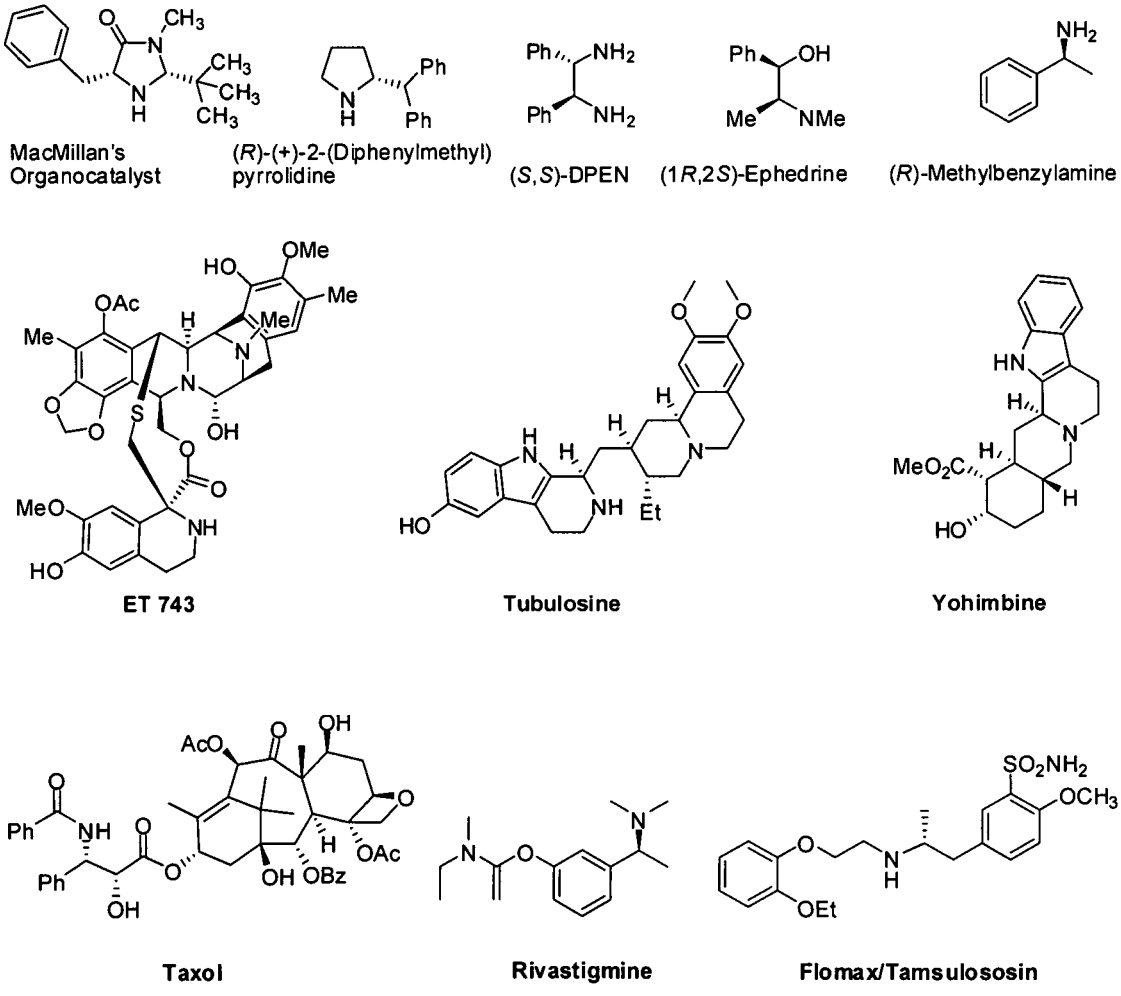
There is no doubt that asymmetric hydrogenation is a major branch of asymmetric catalysis.[6] Asymmetric hydrogenation is one of the most straightforward and efficient methods to produce enantiomerically pure compounds in both industrial scale and laboratory scale. Asymmetric hydrogenation generally refers to addition of H_2 to one of the faces of a prochiral, unsaturated C=C, C=O or C=N double bonds to generate a chiral products with high enantioselectivity. The first major breakthrough occurred in the early 1970s, when Knowles and Horner et al independently demonstrated that rhodium complexes containing chiral phosphine ligands were able to catalyze the enantioselective hydrogenation of a prochiral olefinic substrate, generating a chiral product with excellent enantioselectivity (ee's up to 88%).[10-13] Following the discovery of asymmetric hydrogenation, the first industrial process for the synthesis of

L-dopa, an anti-Parkinson drug, was generated by using a chiral Rh-phosphine catalyzed hydrogenation of a prochiral enamide.[14] Subsequently, thousands of publications have recorded the development of catalytic systems containing chiral ligands for asymmetric hydrogenation of a wide range of prochiral alkenes, ketones and ketimines, and up to 100% ee of products have been obtained.[2,6,8,9,15] Simultaneously, notable understanding of mechanistic pathways of asymmetric hydrogenation has been made by several groups.[6] Although noteworthy progress has been achieved in asymmetric hydrogenation, further extension of its utility is desired, particularly in the area of amine synthesis.

1.2 Importance of Chiral Amines

Chiral amines are one of the most important functionalities in fine chemical, agrochemical, and pharmaceutical products (Scheme 1-1).[16] Because nitrogen-containing amines have the properties of hydrogen bonding, basicity and nucleophility, structurally less complex chiral amines have frequently been used as chiral auxiliaries, ligands and catalysts. For instance, MacMillan's organocatalyst (2*R*,5*R*)-2-*tert*-butyl-3-methyl-5-phenylmethyl-4-imidazolidinone, (*R*)-(+)-2-(diphenylmethyl)pyrrolidine, and (*S*,*S*)-DPEN are employed as a chiral organocatalyst,[17,18] chiral solvating agent,[19] or chiral ligand,[20] and (1*S*,2*S*)-ephedrine and (*R*)-methylbenzylamine are usually used as chiral auxiliaries[16] or resolution reagent.[21] On the other hand, chiral cyclic amines, such as tetrahydroisoquinoline and tetrahydro-β-carboline frequently appear in natural products and biologically important molecules which display high bioactivity. For example, marine alkaloid Et 743, a

potent antitumor drug target, contains three chiral tetrahydroisoquinoline rings.[22] Containing one tetrahydroisoquinoline ring and one tetrahydro-β-carboline ring, tubulosine also displays high antitumor activity.[23] A further example is yohimbine, which contains similar units and is an antagonist for the serotonin



Scheme 1-1. Representative examples of chiral amines.

2B receptor.[24] In addition, α-branched acyclic amines also ubiquitously exist in chiral amine-containing pharmaceutical drug targets. α-Branched amine referes to amine having α-carbon sterocenters. Representative examples include the natural product

Taxol,[25] pharmaceutical target Rivastigmine[26] and billion-dollar drug Flomax (Tamsulososin).[27] Owing to chiral amines widely existing in pharmaceuticals and natural products, the development of efficient methodologies to generate chiral amines is still desired, particular in generating on an industrial scale. The processes for the synthesis of chiral amines are generally based on three chemical strategies; resolution of racemic amines, chemical transformation from a chiral precursor in which the chiral auxiliary group could be removed after formation of diastereoisomers, and enantioselective catalysis.

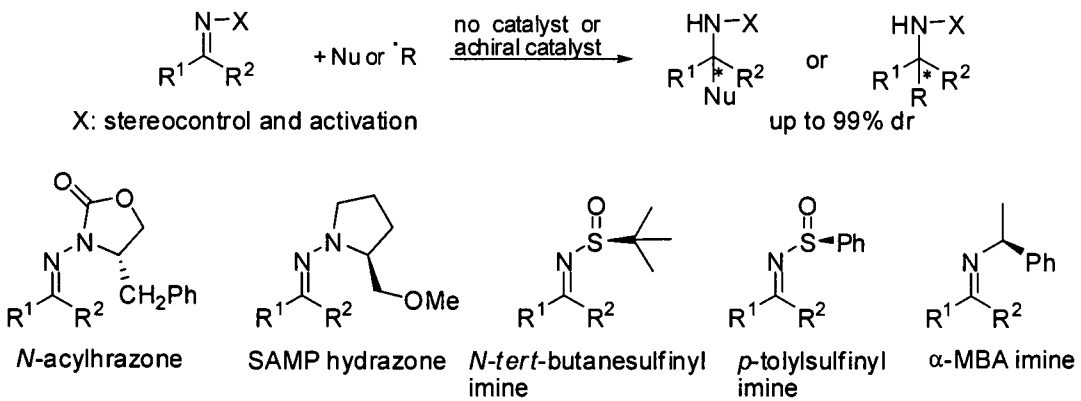
1.3. Methods of Chiral Amine Synthesis

Enantiomerically enriched amines can be generated by diastereoselective carbanion addition to chiral aldimines or ketimines, asymmetric catalytic synthesis or reduction of ketimines with a chiral stoichiometric reagent.[2,8] Based on these chemical transformations, numerous approaches have been developed in the past few decades. The following section provides a summary on methods for synthesis of enantiomerically enriched amines.

Synthesis of Chiral Amines by Auxiliary Controlled Reaction

Addition to C=N double bonds with a chiral auxiliary provides an effective approaches for the development of synthetic route to enantiomerically enriched amines. Several types of chiral imines have been developed so far, such as chiral *N*-acylhydrazones, SAMP hydrazone, *p*-tolylsulfinyl imine and α-MBA imine.[2,3,8,16,28-30] These chiral imines have served important roles in the early

development of synthetic route to produce chiral amines. The chiral *N*-acylhydrazone could go through addition reaction with a range of partners, including radicals, allylsilanes, allyindiums, siyl enol ether, and hydride donors with up to 99% *de*, the resulting diasteroisomers can be converted to chiral amines by using samarium diiodide (SmI_2) or borane cleavage of the N-N bond (Scheme 1-2).[28] Chiral amines with up to 99% ee also can be generated from chiral SAMP hydrazone, *N-tert*-butanesulfinyl imines and *p*-tolylsulfinyl imines via the addition of organometallic reagents to C=N bonds followed by deprotection of chiral auxiliary groups.[29] Chiral amines were also obtained from enantioselective reduction of α-MBA imines and sequent deprotection.[16]

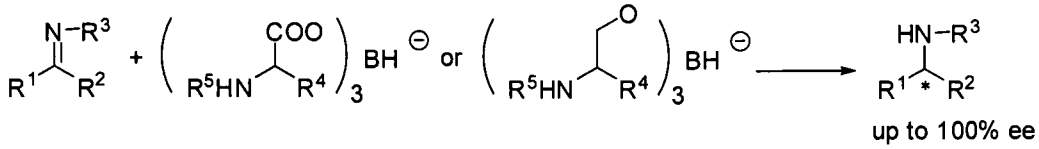


Scheme 1-2. Synthesis of chiral amines from chiral precursors.

Synthesis of Chiral Amines by Stoichiometric Hydride Reduction

Chiral borane-based hydride reagents are generally used for the reduction of cyclic and acyclic ketimines to generate enantiomerically enriched amines.[2,6,8,16,31] These reagents can be prepared from commercially available amino acids or amino alcohols

with borane.[31] Good to excellent ees of cyclic and acyclic amines have been obtained by using preformed chiral borane-based hydride reagents in the reduction of ketimines (Scheme 1-3).



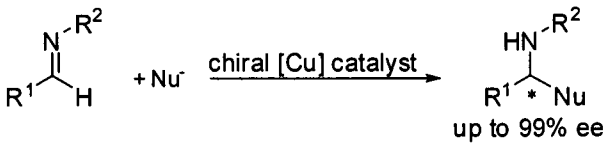
Scheme 1-3. Synthesis of enantiomerically enriched amines from chiral reagents.

Synthesis of Chiral Amines by Asymmetric Catalysis

Catalytic systems have displayed advantages in the synthesis of enantiomerically enriched amines in the past few years. Owing to the importance of chiral amines, a lot of enantioselective catalytic systems have been developed in order to generate amines with excellent enantioselectivity. However, there are only several direct and common approaches to generate chiral amines, which include catalytic enantioselective alkylation of imines, Mannich-type reactions, cyanation of imines, hydrosilylation of imines, transfer hydrogenation of ketimines, and hydrogenation.[2,8] The following section provides an introduction to the catalytic enantioselective systems except for transfer hydrogenation and hydrogenation of ketimines, which will be dealt with separately.

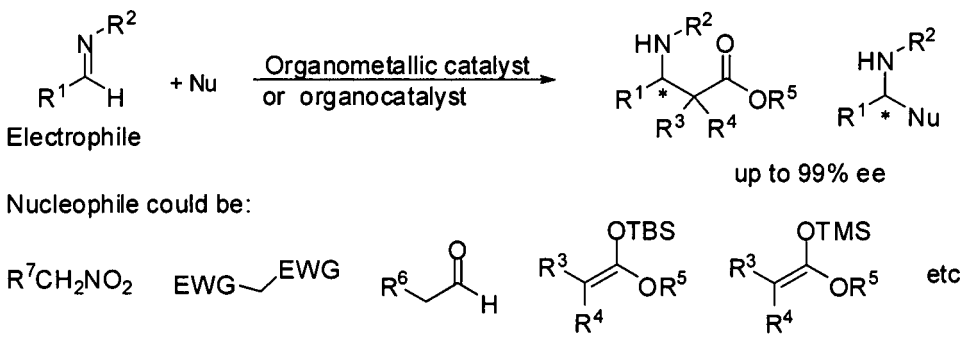
The asymmetric alkylation of imines is one of the fundamentally important reactions, in which nucleophiles selectively add to one of the faces of prochiral C=N double bonds in the presence of a catalytic amount of catalyst (Scheme 1-4).[2,3,8,32,33] In this reaction, the nucleophiles are generally organometallic reagents, such as, organozinic,

organolithium, and organoaluminum, or electron rich aromatic compounds, such as, indole, pyrrole, furan, and thiophene; and chiral organocopper complexs are normally used as catalysts.[33] Although the best enantioselectivity can reach up to 99% ee, only a few asymmetric catalysts are available for this reaction, and application of enolizable imines is still sometimes problemtic.



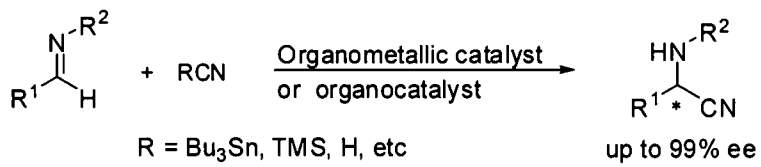
Scheme 1-4. Synthesis of chiral amines by asymmetric alkylation reaction.

Asymmetric Mannich reactions are one of the most powerful approaches to access chiral β-amino carbonyl compounds and other chiral amino derivatives.[2,3,8,34-37] Chiral amines can be produced by nucleophile addition to electrophilic C=N double bonds in the presence of a chiral organometallic catalyst or organocatalyst with up to 99% ee (Scheme 1-5). Asymmetric organocatalysis of this reaction has greatly enlarged the scope of nucleophiles from silyl enolates, nitro-substrates, nucleophile with electron withdrawing group, and aldehydes which can form enamine as a nucleophile in the presence of catalytic amount of amine.



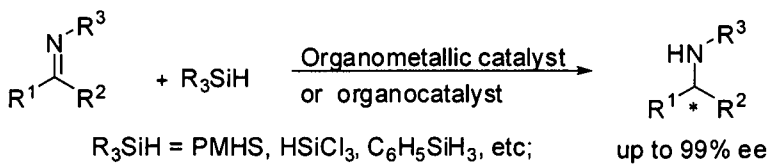
Scheme 1-5. Synthesis of chiral amines by asymmetric Mannich reaction.

The cyanation of imines, generally called the Strecker reaction, is also one of the most useful reactions. Chiral α-amino nitriles can be obtained by enantioselective addition of cyanide to C=N double bonds with up to 99% ee (Scheme 1-6).[2,3,8,38-40] The cyanide source could be Bu_3SnCN, HCN or TMSCN, and the catalyst could be chiral Lewis acids, organometallic catalysts or hydrogen bonding organocatalysts. The resulting α-amino nitrile can be converted to an α-amino acid via acid hydrolysis of the nitrile group to carboxylic acid.



Scheme 1-6. Synthesis of chiral amines by asymmetric cyanation of imines.

Asymmetric hydrosilylation of ketimines is another direct method to produce chiral amines. The ketimine can be reduced by polymethylhydrosiloxane (PMHS), $HSiCl_3$ or $C_6H_5SiH_3$ in the presence of a catalyst promoting and inducing chiral hydrosilylation (Scheme 1-7).[2,3,8,41,42] Chiral titanocene, iridium and copper complexes have shown excellent enantioselectivity for cyclic and acyclic ketimines, the highest ee being up to 99%.[2,8] Hydrogen bonding organocatalysts also showed excellent enantioselectivity for reduction of ketimines, the highest ee being again up to 99%.[43]



Scheme 1-7. Synthesis of chiral amines by asymmetric hydrosilylation of ketimines.

2. Asymmetric Hydrogenation of Imines and Imino Esters

2.1 Introduction

Catalytic asymmetric hydrogenation (including transfer hydrogenation) of imines, oximes, hydrazones, and imino esters is one of the most direct and efficient methods for the synthesis of chiral amines and their derivatives.[6] Fourty years ago, there were only a few methods to synthesize enantiomerically enriched amines *via* enantioselective heterogeneous hydrogenation of oximes or dioximes; the method uses Pt black, Pd/C or Raney nickel together with chiral auxiliaries.[44,45] However, the approach was only applied to a very few substrates, and gave amines in low enantioselectivities and the results could not always be reproducible.[44,45] Boyle, Scorrano and Botteghi et al independently reported the first example of Rh/Ru-phosphine complex-catalyzed asymmetric hydrogenation of a carbon-nitrogen double bond to produce enantiomerically enriched amines with less than 22% ee during 1974-1975.[46-48] In 1984, a remarkably improved enantioselectivity was achieved by using Rh-BDPP complex-catalyzed hydrogenation of acetophenone *N*-benzylimine to give the corresponding amine in 72% ee.[49] In the 1990s, several remarkable progresses on asymmetric hydrogenation of a range of imines were made by Noyori, Buchwald and Blaser et al by using Ru-Ts-DPEN,[50] Ti[51-53] and Ir-diphosphine complexs,[54-56] respectively. The first successful manufacture of the herbicide (*S*)-metolachlor was achieved by using Ir-diphosphine-catalyzed hydrogenation of corresponding imine in 1999.[54]

Although some remarkable progress has been achieved so far, only a few chiral

catalysts have found successful applications in enantioselective hydrogenation of C=N functions. Several chiral Ru, Rh, Ti, Ir, Pd, and Au complexs have been developed for the hydrogenation of C=N functions so far. Since the earliest application of $[Rh(NBD)(DIOP)]^+ClO_4^-$ and $H_4Ru(CO)_8(DIOP)_2$ in asymmetric hydrogenation of imines and oximes, a few chiral Rh/Ru complexes have been developed,[47,48] such as $RuCl_2$(diphosphine)(diamine), Ru(Cymn)(diamine)Cl, and cationic $[CpRu(diphosphine)]^+$ and $[Rh(COD)(diphosphine)]^+$ with different anions.[6] In these catalysts, Noyori's complex Ru(Cymn)(Ts-DPEN)Cl showed good enantioselectivity and activity for transfer hydrogenation of imines.[50] Chiral titanocene complexes, one of the successful catalysts, showed high enantioslectivies for *N*-alkyl ketimines hydrogenation; however, the catalysts were difficult to handle and the activity of catalysts was not so high for hydrogenation of imines.[51-53] Thus far, a few chiral iridium complexes have been developed and become more popular a choice for hydrogenation of imines since the first Ir-BDPP complex-catalyzed imine hydrogenation was reported in 1990.[6,56] Recently, Pd complexs have been employed for imine and imino ester hydrogenation to give amines and amino esters with good to excellent enantioselectivies.[57] And more recently, Au-Me-DuPhos also showed good acitivity and enantioselectivity for hydrogenation of acetophone *N*-benzylimine.[58] However, all of these catalysts generally show either unsatisfactory ee's or narrow scope of substrates.

More highly active and selective catalysts are desired for asymmetric hydrogenation of imines. It has been known that the catalytic property of a chiral metal

catalyst is determined by the metal, chiral ligand and the anion of the complex. Transition metals are generally utilized for preparing catalysts for hydrogenation of imines. Different transition metals usually show special activities and selectivies in the catalytic hydrogenation. For most chiral complexs, chiral ligands also play a very important role in the asymmetric catalytic systems because the product chirality is transfered from the chiral ligand and the catalytic activitiy of complex highly depends on the coordinating ligand. Recently, some research groups have found that the anion of a complex can highly affect catalytic activities and selectivies in many asymmetric reactions, and even a chiral anion of achiral complex could efficiently transfer chirality from the anion to the product.[59] Therefore, metal, ligand and anions are considered to be three very important parts of the strategy in the development of highly efficient catalyst.

Highly selective and wide scope reductive amination *via* hydrogenation of imines is still considered a big challenge in asymmetric catalysis. Asymmetric hydrogenation of imines is far less developed than the hydrogenation of ketones and olefins, because there are more unsolved problems in imine hydrogenation.[6] There are numerous successful chiral catlysts for diverse ketone and olefin hydrogenation. However, most of those catalysts are less effective for the various C=N functional groups in terms of enantioselectivity (ee, %), productivity (turnover number, TON), substrate to catalyst ratio (SCR) or activity (turnover frequency, TOF). This is probably because several aspects affect the hydrogenation of C=N functions. The first is that the catalysts might be poisoned by the imine substrate, or amine product, because the nitrogen atom may

strongly coordinate to the metal centre, resulting in catalyst deactivation. The second is that the C=N functional groups are easy to tautomerize to *syn/anti* isomers. The third is that acyclic C=N functional substrates often easily undergo hydrolysis during the reduction. The following sections provide a summary on the state of the art enantioselective hydrogenation (including transfer hydrogenation) of various classes of C=N functions by using special chiral metal complexs.

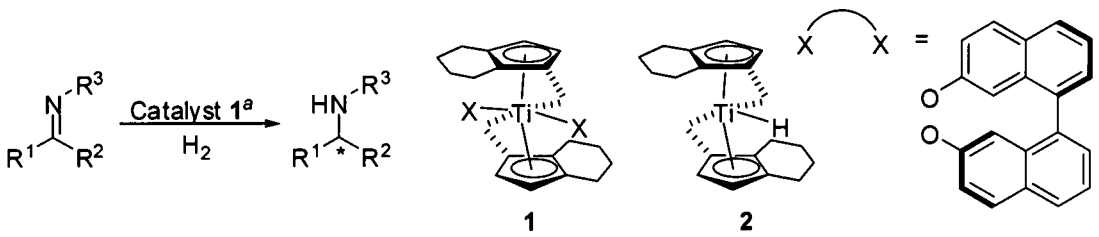
2.2 Transition Metal-catalyzed Asymmetric Hydrogenation

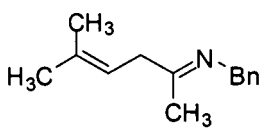
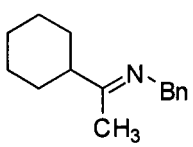
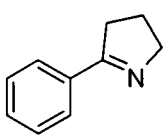
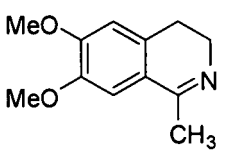
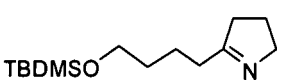
2.2.1 Asymmetric Hydrogenation of Imines with Ti Complexes

Buchwald and coworkers demonstrated a highly efficient, enantioselective hydrogenation of imines by using a chiral titanocene precatalyst **1**,[51-53] first synthesized by Brintzinger.[60] The titanocene catalyst showed good to excellent enantioselectivities for a range of acyclic and cyclic imines, especially for cyclic ones. Representative results are listed in Table 1-1.[51,52] Produced from precatalyst **1**, titanocene (III) hydride species **2** was assumed to be the active intermediate in the catalytic cycle. Acyclic amines were obtained in good ee's under 138 bar hydrogen pressures; however, the enantioselectivities were significantly decreased when lowering the hydrogen pressure (entries 1 and 2). Conversely, cyclic amines were obtained in excellent ee's and good yields under either high or low hydrogen pressure (entries 3-5). Compared with acyclic imines, some higher ee's were obtained for cyclic imines by using the catalyst **1**. A probable explanation is that cyclic imines only exist as a single anti isomer; on the contrary, acyclic imines exist as a mixture of syn and anti-isomers during the reaction.

Notably, the catalyst showed good enantioselectivity for different types of cyclic and acyclic imines, and could tolerate different functional groups, such as alkene and TBDMS. However, its potential application is rather low, because TOF is rather low and the catalyst is difficult to operate.

Table 1-1. Asymmetric hydrogenation of imines with chiral Ti Complex



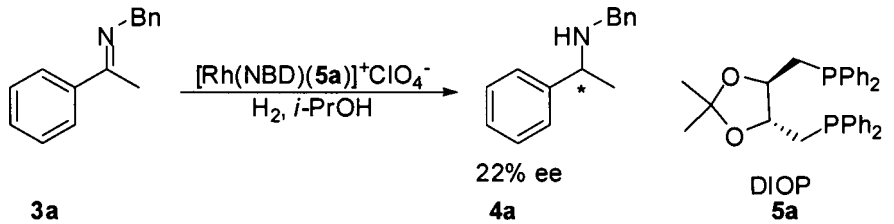
entry	substrate	anti/syn	P(H_2) (bar)	catalyst equiv.	yield (%)	ee (%)
1		3.3:1	138	0.1	64	62
2		17:1	138 34	0.05 0.05	93 85	76 43
3		/	138 34 6	0.05 0.05 0.01	77 86 84	98 99 99
4		/	138 6	0.05 0.05	82 79	98 95
5		/	6	0.05	82	99

[a] The catalyst precursor **1** was activated *in situ* by treatment of 2 equiv. of BuLi and 3 equiv. of $PhSiH_3$.

2.2.2 Asymmetric Hydrogenation of Acyclic Imines with Rh Catalysts

Although chiral titanocene catalyst has shown good enantioselectivities for various acyclic and cyclic imines, chiral Rh and Ir complexs are still preferred in industrial processes and academic research. So far, several late transition metals including Rh, Ir, Ru, Pd and Au have been investigated for asymmetric hydrogenation of imines, and imino esters to generate chiral amines with good ee's.

The earliest report on asymmetric hydrogenation of acyclic imines was from Scorrano's group in 1975 and used a chiral rhodium catalyst (Scheme 1-8).[47] Enantiomerically enriched amine **4a** was obtained in 22% ee and 67-80% yield by using catalytic amount of $[Rh(NBD)(\mathbf{5a})]^+[ClO_4]^-$ to hydrogenate **3a** in isopropanol (IPA). A lower ee of **4a** was observed when ethanol or methanol was used as a solvent.



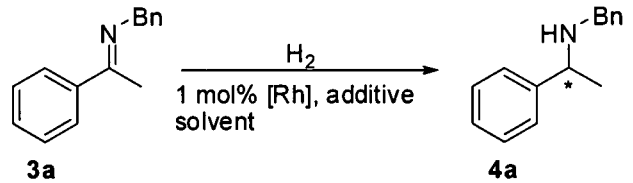
3a 22% ee **4a** DIOP **5a**

Scheme 1-8. The earliest asymmetric hydrogenation of **3a** with Rh-**5a**.

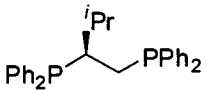
Although the first example of hydrogenation of acyclic imine did not achieve good ee, significantly improved ee's were subsequently obtained from several research groups (Table 1-2). Takach and King et al investigated a series of chiral diphosphine ligands; they found the corresponding chiral amine **4a** could be obtained in 66% ee (100% conversion) and 72% ee (98% conversion) from **3a** by using the in situ catalyst derived from $[Rh(NBD)Cl]_2$ and ligand **6** and **7**, respectively (entries 1 and 2).[49] Bakos and coworkers also explored the imine **3a** hydrogenation by using a chiral

Rh-BDPP complex (Table 1-2).[61,62] In Bakos's system, they found the reaction highly depended on solvent and temperature. A 13% ee was obtained in a mixture solvent (benzene/methanol = 4:1); but a 73% ee was obtained in pure methanol (entries 3 and 4). Lowering the reation temperature, the ee of amine **4a** was improved to 83% at 0 °C in methanol (entry 5).

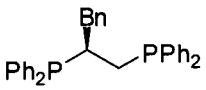
Table 1-2. Improved enantioselectivities of hydrogenation of **3a**



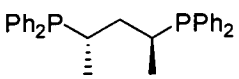
3a **4a**



(*R*)-Valphos
6



(*R*)-Benzphos
7



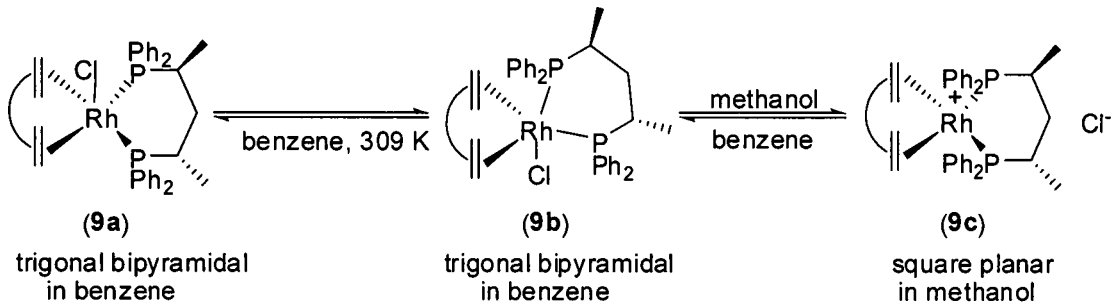
(*S,S*)-BDPP
8a

entry	ligand	additive	temperature and solvent	conv. %	ee %	config.
1[a]	**6**	/	25 °C, benzene/methanol (1/1)	100	66	*S*
2[a]	**7**	/	25 °C, benzene/methanol (1/1)	98	72	*S*
3[b]	**8a**	Et_3N	20 °C, benzene/methanol (4/1)	100	13	*R*
4[b]	**8a**	Et_3N	20 °C, methanol	100	73	*R*
5[b]	**8a**	Et_3N	0 °C, methanol	55	83	*R*

[a] The *in situ* catalyst was used; [b] prepared catalyst was used.

In Bakos's catalytic system, the enantioselectivity highly depended on solvent and reaction remperature. Further studies by ^{31}P NMR of the complex {Rh(NBD)[(*S,S*)-**8a**]}Cl in solution indicate that the complex structure was sensitive to solvent and temperature (Scheme 1-9).[62] The equilibrium of **9a** and **9b** exists in

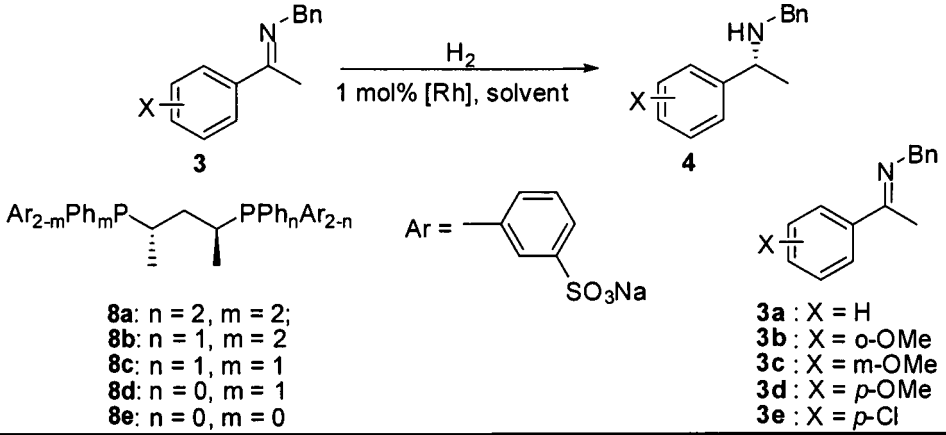
benzene at room temperature; and the complex might be converted into the square planar **9c** in methanol. Furthermore, the equilibrium between **9b** and **9c** also exists when the solution changes from benzene to the polar methanol. The low optical yield is caused by the mixture of quasi-symmetrical **9a** and **9b** when **3a** was hydrogenated in benzene (Table 1-2, entry 3). Conversely, The C_2 symmetric **9c** was considered to be a stable intermediate in methanol, which led to high optical yield of amine **4a** (Table 1-2, entries 4 and 5).



Scheme 1-9. Bakos's investigation of the conformation of {Rh(NBD)[(*S*,*S*)-**8a**]}Cl in various solvents.

Several water soluble chiral ligands **8b**, **8c**, **8d** and **8e**, containing partially or fully sulfonate salt, were examined for asymmetric hydrogenation of acyclic imines in a two-phase system by Sinou,[63] Bakos[64] and de Vries's[65] research groups independently. They demonstrated that ee's of amine are strongly dependent on sulfonation degree of the diphosphine ligands (Table 1-3).[63-65] Bakos et al found that phosphine ligand with about 1.65 sulfonation degree, which is composed of a mixture of epimers, afforded the best enantioselectivities, whilst around full sulfonation showed the lowest enantioselectivities for **3a** hydrogenation. Several enantiomerically riched amines were obtained in 89-96% ee's by using Rh-**8** complexes of 1.65 sulfonation degree.

Table 1-3. Asymmetric hydrogenation of acyclic imines with catalyst Rh-**8**



8a: n = 2, m = 2;
8b: n = 1, m = 2
8c: n = 1, m = 1
8d: n = 0, m = 1
8e: n = 0, m = 0

3a : X = H
3b : X = o-OMe
3c : X = m-OMe
3d : X = *p*-OMe
3e : X = *p*-Cl

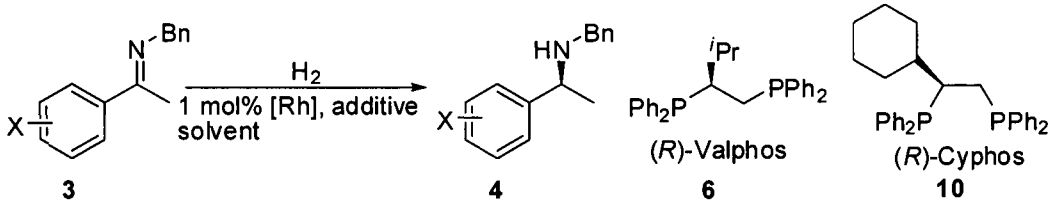
entry	substrate	sulfonation degree	solvent	conv. (%)	ee [a] (%)	config.	ref
1	**3a**	4 (**8e**)	EtOAc-H_2O	100	34 [b]	*R*	63
2	**3a**	1.86	EtOAc-H_2O	100	58 [b]	*R*	63
3	**3a**	3.75	EtOAc-H_2O	55	19	*R*	64
4	**3a**	1.41	EtOAc-H_2O	96	96 (88) [b]	*R*	64
5	**3a**	1.65	EtOAc-H_2O	94	96 (95) [b]	*R*	64
6	**3b**	1.65	EtOAc-H_2O	96	95 (86) [b]	*R*	64
7	**3c**	1.65	EtOAc-H_2O	93	89 (86) [b]	*R*	64
8	**3d**	1.65	EtOAc-H_2O	94	91 (92) [b]	*R*	64
9	**3a**	1 (**8b**)	EtOAc-H_2O	85	94	*R*	65
10	**3d**	1 (**8b**)	EtOAc-H_2O	>98	92	*R*	65
11	**3e**	1 (**8b**)	EtOAc-H_2O	>98	92	*R*	65

[a] Ee was determined by ^{1}H NMR; [b] Ee was determined by HPLC

de Vries and coworks separated the mixture of epimers by column chromatography, and the mono- and di-sulfonated **8b** and **8c** were obtained and characterized. Rh-**8b** complex showed a similar enantioselectivity to the Rh-**8** complex of 1.65 sulfonation degree in hydrogenation of **3a** (entry 9). Furthermore, FAB-MS spectra showed the

SO_3^- group of **8b** acts as a counteranion of catalyst Rh-**8b**.

Table 1-4. Halide effect on enantioselective hydrogenation of acyclic imines



3 **4** **6** **10**

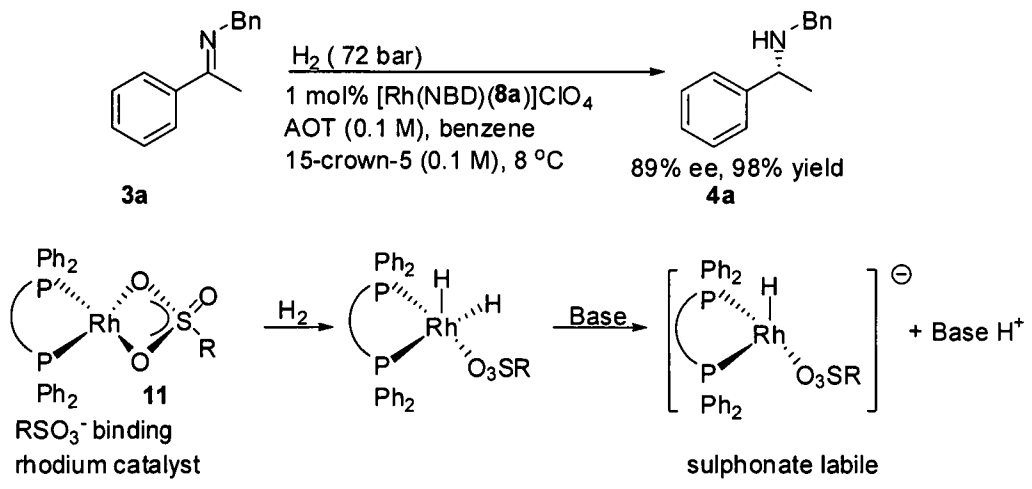
entry	substrate	ligand	additive	temperature and time	conv. (%)	ee (%)	config.	ref
1 [a]	**3a**	**6**	/	50 °C, 8h	90	15.5	*R*	49
2 [a]	**3a**	**6**	KCl	50 °C, 8h	100	35.5	*S*	49
3 [a]	**3a**	**6**	KI	50 °C, 8h	93	47.8	*S*	49
4 [b]	**3a**	**10**	/	20 °C, 18h	>99	67	*S*	66
5 [b]	**3a**	**10**	KI	20 °C, 90h	>99	79	*S*	66
6 [b]	**3b**	**10**	KI	20 °C, 120h	>99	71	*S*	66
7 [b]	**3d**	**10**	KI	20 °C, 72h	>99	84	*S*	66
8 [b]	**3d**	**10**	KI	-25 °C, 144 h	>99	91	*S*	66

[a] Prepared catalyst [Rh(NBD)(**6**)]ClO_4; [b] Catalyst in situ prepared from $[Rh(NBD)Cl]_2$ and **10**.

Takach and King et al found that a halide additive exerted a marked influence on catalytic activity and enantioselectivity in the Rh-phosphine catalyzed hydrogenation of imines. (Table 1-4, entries 1-3).[49] As shown, the catalyst [Rh(NBD)(**6**)][ClO_4] displayed a low enantioselectivity for hydrogenation of **3a**, affording the amine **4a** with only 16% ee. However, both KCl and KI significantly improved the ee's of amines **4a**, from 16% to 36% and 48%, respectively. Interestingly, the configuration of **4a** was reversed in the presence of halide additive. A 67% ee was obtained by using the in situ

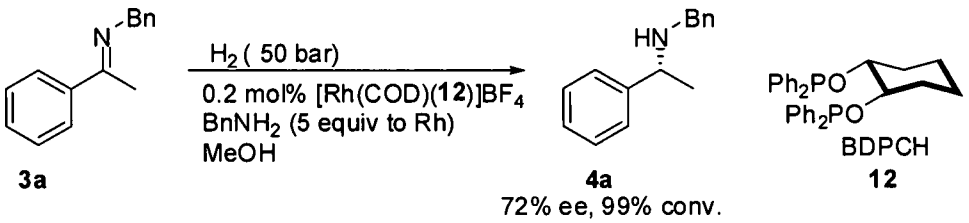
neutral catalyst Rh-**10**, and the enantioselectivity was improved to 79% ee in the presence of KI (entries 4 and 5).[66] Using the chiral Rh-**10** catalyst with co-catalyst KI, two enantiomerically enriched amines **4b** and **4d** were obtained in up to 91% ee (entries 6-8).[66]

Osborn et al investigated the additive effect of the reverse aggregation of sodium bis(2-ethyl-hexyl) sulfosuccinate (AOT) on the hydrogenation of imine **3a** (Scheme 1-10).[67] They found the AOT greatly enhanced enantioselectivity in the $[Rh(NBD)(\mathbf{8a})]^+[ClO_4]^-$ catalyzed hydrogenation of **3a**, the ee of **4a** being increased from 68% in neat benzene to 89% in the presence of 0.1 M AOT and 0.1 M 15-crown-5. Further studies with ^{31}P NMR and MS revealed that the sulfonate anion was bound to the Rh^I center in a bidentate fashion **11** but was rapidly exchanging on and off the catalyst. They considered that the reaction took place in a monohydride pathway in the presence of sulfonate in nonpolar solvent.



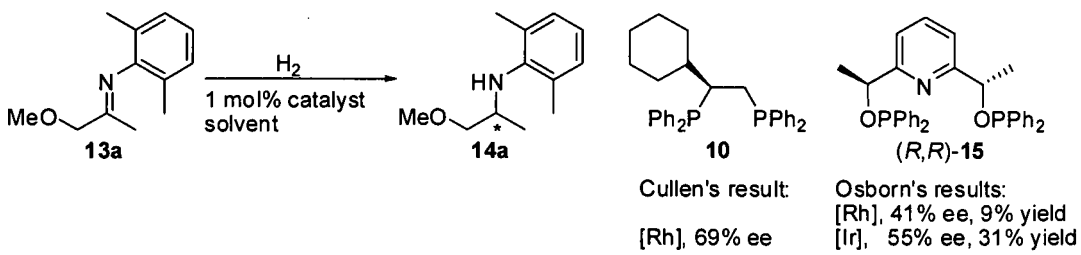
Scheme 1-10. Asymmetric hydrogenation of **3a** by using Rh-**8a** with additives.

Borner and coworkers explored a range of Rh(I)-diphosphine and diphosphinite complexes for **3a** hydrogenation (Scheme 1-11).[68] In their studies, they found that rhodium complex with five and six-membered chelates or electron-rich alkylphosphines showed low activity for imine **3a** hydrogenation. However, Rh-complex based on the chiral diphosphite **12** could rapidly transform the imine **3a** to the desired amine **4a** in 72% ee within 5 hours.



Scheme 1-11. Asymmetric hydrogenation of imine **3a** with Rh-**12**.

James et al explored a range of Rh-diphosphine complexes for the hydrogenation of an important acyclic imine **13a** (Scheme 1-12).[69] They found that the combination of a Rh (I) precursor with (*R*)-**10** showed the best enantioselectivity for **14a**. Osborn and coworkers also investigated the same hydrogenation by using various combination of diphosphine or diphosphite with Rh(I) or Ir(I) precursor (Scheme 1-12).[70] In their investigations, the Ir-**15** complex presented the highest activity and enantioselectivity for **13a** hydrogenation.



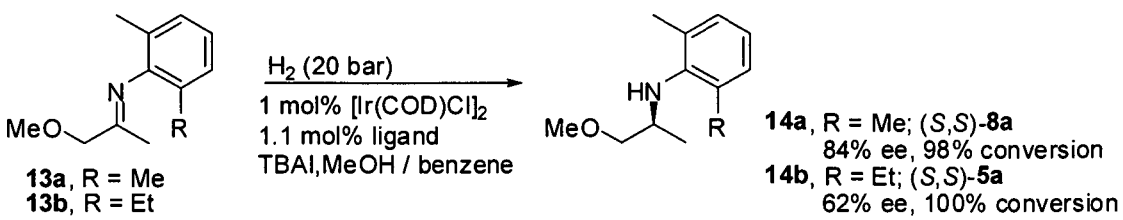
Scheme 1-12. Asymmetric hydrogenation of imine **13a**.

2.2.3 Asymmetric Hydrogenation of Acyclic Imines with Ir Catalysts

Recently, chiral Ir catalysts have been widely used for enantioselective hydrogenation of imines both in academic research and industrical process, because chiral Ir catalysts are stable and easy to handle and show high activities and good enantioselectivities in hydrogenation of imines.[6] Classified according to the type of chiral complex, four types of Ir-complexes have been developed for a range of of imines, which show good conversion and moderate to excellent ee's.

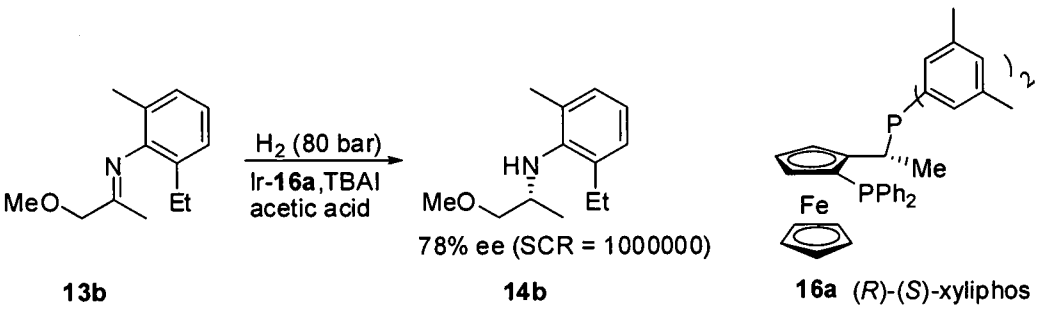
Chiral Diphosphine Ligands

Blaser and coworkers discovered a highly efficient, enantioselective catalytic system for the hydrogenation of *N*-arylketimines **13a** and **13b** to produce the corresponding chiral amines **14a** and **14b** in 84% ee (98% conversion) and 62% ee (100% conversion) by using an in situ chiral Ir-diphosphine catalyst (Scheme 1-13).[56] The amine **14b** is an important intermediate for the herbicide Metolachlor. A range of chiral diphosphine ligands in combination with $[Ir(COD)Cl]_2$ were investigated. They found that the conformationally flexible six or seven memberred metallacycle (BDPP **8a**, DIOP **5a**, BPPM) diphosphinoiridium complexs presented higher activities and enantioselctivities. A further investigation found that the anion of halide additive also markedly influenced the enantioselectivities and activities of the reaction.



Scheme 1-13. Asymmetric hydrogenation of **13** by using Ir catalysts.

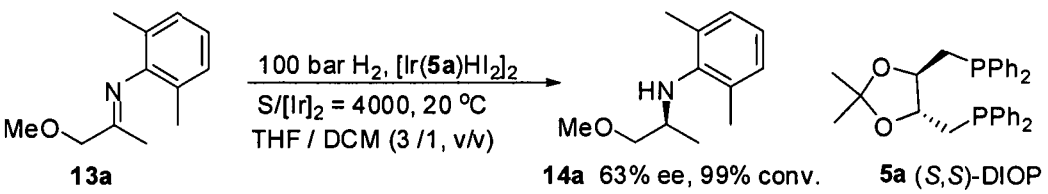
Following their breakthrough in imines hydrogenation, Blaser et al applied their catalytic system to an industrial process by using an iridium catalyst containing **16a** with small amount of acetic acid and iodide as additives (Scheme 1-14).[55] The catalytic system offered a good enantioselectivity and a very high activity with the SCR reaching up to 1000000.



13b **14b** **16a** (*R*)-(*S*)-xyliphos

Scheme 1-14. Blaser's catalytic system for asymmetric hydrogenation of **13b**.

Simultaneously, Osborn and coworkers independently developed a well-defined chiral $[Ir(III)(P\text{-}P)HI_2]_2$ complex for enantioselective hydrogenation of *N*-arylketimines **13a** (Scheme 1-15).[71] Prepared from $[Ir(COD)(P\text{-}P)]BF_4$ and excess LiI in acetone, the preformed catalyst showed good activities (SCR = 4000) with moderate to good enantioselectivity for the hydrogenation of **13a** to the corresponding amine **14a**.

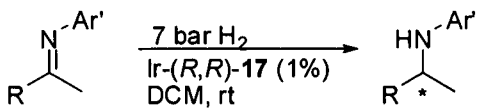


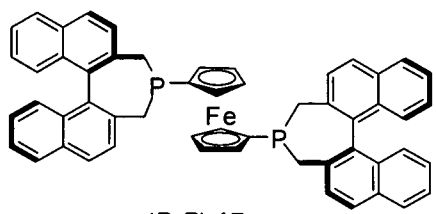
13a **14a** 63% ee, 99% conv. **5a** (*S*,*S*)-DIOP

Scheme 1-15. Asymmetric hydrogenation of **13a** with $[Ir(\mathbf{5a})HI_2]$.

Although some remarkable progresses in diphosphinoiridium complex-catalyzed hydrogenation of imines have been achieved by Blaser and Osborn, only a few imines were successfully hydrogenated in high ee's.[55,71] Zhang and co-workers developed a new chiral ligand (*R*,*R*)-**17** for enantioselective hydrogenation of both aromatic and alphatic *N*-arylimines, generating amines with up to 99% ee (Table 1-5).[72] The catalyst showed high activities and enantioselectivities for aryl methyl ketimines, but lower enantioselectivities of 8% ee to 31% ee for alkyl methyl ketimines. Iodide additives also promoted the reduction and improved enantioselectivities. The observation was consistent with the results of Blaser and Osborn et al. A proposed mechanism suggests that iodide plays two roles during the reduction, one being oxidation of Ir(I) to Ir(III) and activation of the catalyst, another being assisting heterolytic splitting of hydrogen.

Table 1-5. Enantioselective hydrogenation of acyclic imines with the catalyst Ir-**17**



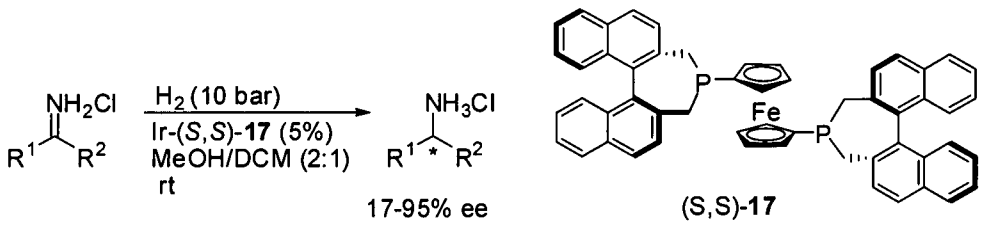


(*R*,*R*)-**17**

entry	R	Ar'	t (h)	conv. (%)	ee (%)
1	Ph	Ph	40	100	84
2	Ph	2,6-dimethyl-C_6H_3	44	77	>99
3	4-CF_3-C_6H_4	2,6-dimethyl-C_6H_3	44	80	99
4	*i*-Pr	2,6-dimethyl-C_6H_3	44	29	23
5	Ph	4-MeO-C_6H_4	14	100	81

Quiet recently, Gosselin and Zhang et al developed a more efficient enantioselective catalytic system by using the Ir-(*S*,*S*)-**17** catalyst (Table 1-6),[73] which hydrogenates unprotected N-H imines to form free amino salts. A range of pure or mixture solvents and counteranions of iminium salts were investigated for the optimization of conditions.

Table 1-6. Enantioselective hydrogenation of unprotected N-H imines with Ir-**17**



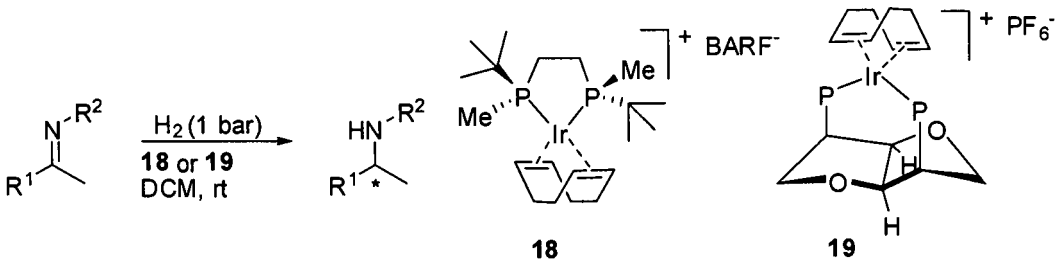
entry	R^1	R^2	yield(%)	ee (%)	config.
1	4-MeC_6H_4	Me	95	95	*R*
2	C_6H_5	Et	92	86	*R*
3	C_6H_5	*t*-Bu	90	80	*R*
4	4-$CF_3C_6H_4$	Me	93	93	*R*
5	2-MeC_6H_4	Me	92	81	*R*
6	*t*-Bu	Me	90	17	*R*
7	cyclohexyl	Me	91	73	*R*

They found that the mixture solvent of methanol and dichloromethane (2:1) and chloride as counteranion of iminium salts were benefical to enhancement of reactivity and enantioselectivity of the reaction. A series of aryl alkyl and alkyl alkyl unprotected N-H amines were obtained under the optimized conditions in 17-95% ee and 90-95% isolated yield.[73] They found the bulkiness of the R^2 group and the methyl or chloro substituent on R^1 group at the *ortho*-position slightly reduced the ee.[73] However,

substrates having both electron-donating and withdrawing substitutents on the aromatic ring in R^1 were obtained with similarly high enantioselectivities. Their catalyst showed lower enantioselectivities for akyl alkyl imines, however.

Since Osborn et al reported the first [Ir(COD)(P-P)][ClO_4] complex-catalyzed enantioselective hydrogenation with modest activity and enantioselectivity,[70] Imamoto and Dervisi et al have developed competent chiral cationic complexes **18** and **19** with noncoordinating $BARF^-$ and PF_6^- anions for hydrogenation of ayclic imines.[74,75] In Imamoto's study, a series of coordinating anion Cl^-, weakly coordinating anion OTf^-, noncoordinating anion BF_4^-, PF_6^- and $BARF^-$ and various diphosphine ligands were explored for imine hydrogenation.[74] The cationic complex **18** showed the best enantioselectivity and good activity at 1 bar hydrogen pressure. Based on these conditions, a range of aryl methyl amines were obtained in 91-99% yield and 69-99% ee (Table 1-7).[74] However, catalyst **18** showed no activity for the hydrogenation of alkyl methyl imines (entry 3). Dervisi et al explored solvent and pressure effect by using their catalyst **19**.[75] They found that coordinating solvent lowered the catalyst activity and high hydrogen pressure inhibited the catalytic activity as well due to formation of dimeric and trimeric Ir(III) polyhydrides. A range of aryl alkyl amines were obtained in 98-100% conversion and 81-94% ee. However, catalyst **19** showed lower activity and enantioselectivity for hydrogenation of *N*-benzyl imine, affording only 20% conversion and 5% ee. These results show that cationic catalysts with non-coordinating anions have higher activity than the complex containing coordinating anions.

Table 1-7. Enantioselective hydrogenation of acyclic imines with cationic Ir-diphosphine complexes



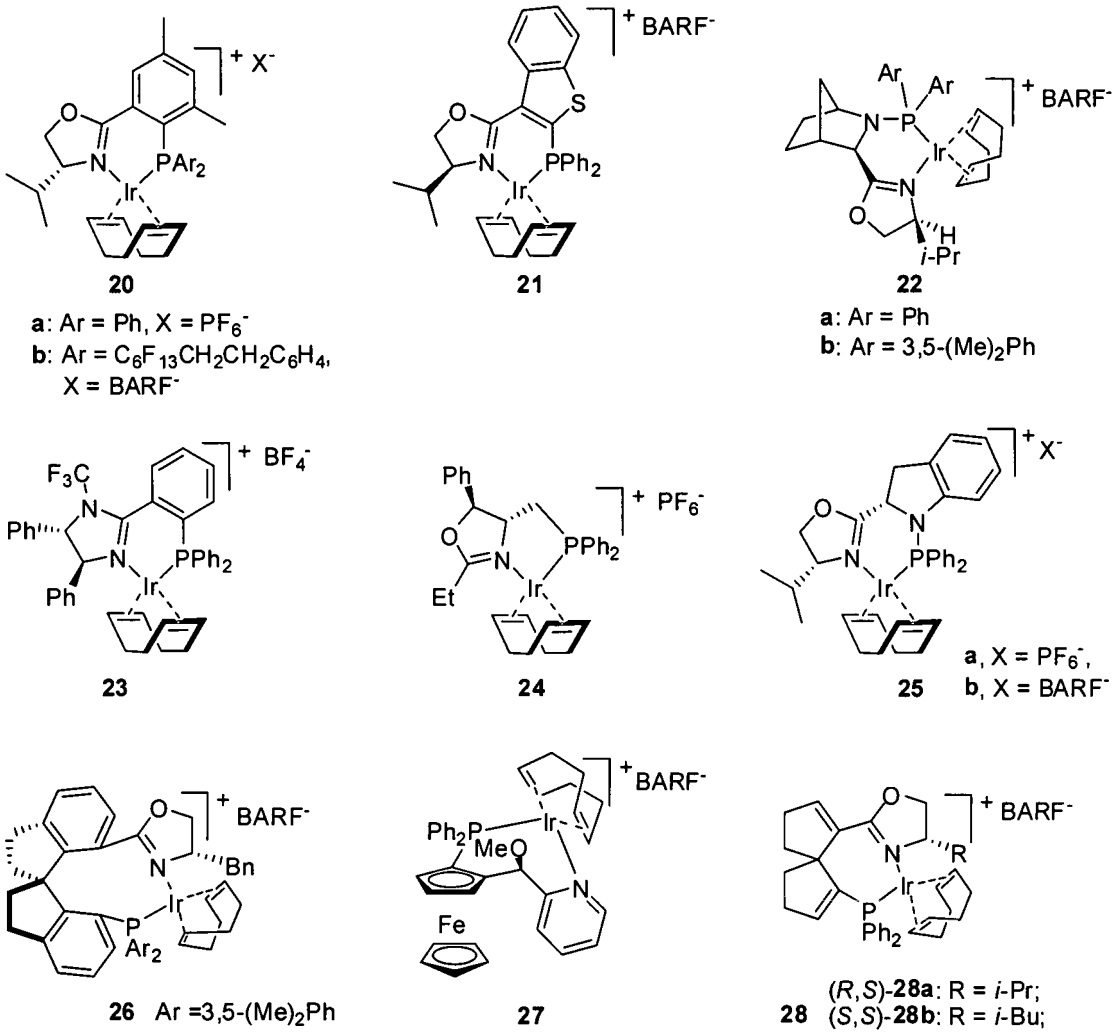
entry	R^1	R^2	catalyst	yield (%)	ee (%)	config.
1	Ph	Ph	**18**	91	86	*R*
2	Ph	4-CF_3-Ph	**18**	95	99	(-)
3	*t*-Bu	Ph	**18**	0	/	/
4	Ph	Ph	**19**	99	84	*R*
5	Ph	4-MeO-Ph	**19**	99	94	(+)
6	Ph	$PhCH_2$	**19**	20	5	*R*

[a] 0.5%; of catalyst **18**; [b] 1%; of catalyst **19**.

Chiral P, N Ligands

Pfaltz and co-workers reported the first chiral cationic Ir-phosphanodihydrooxazole complexes **20a** for enantioselective hydrogenation of imines (Scheme 1-16).[76] The air stable **20a** showed good activities and enantioselectivities for the hydrogenation of *N*-alkyl and *N*-aryl imines (Table 1-8, entries 1 and 2). Coordinating anion and solvent significantly decreased the catalyst activity and enantioselectivity. In their investigation, they also found that the activity and enantioselectivity of the cationic **20a** was markedly influenced by the concentration of substrate and catalyst loading. Thus, the substrate **29** was hydrogenated to the corresponding amine with the ee value improved from 71% to 86% when the concentration of **29** was lowered from 0.22 M to

0.035 M.[76] Catalyst **20a** showed good activity and enantioselectivity for a wide scope of acyclic imines. However, it was less efficient for dialkyl and cyclic imines.

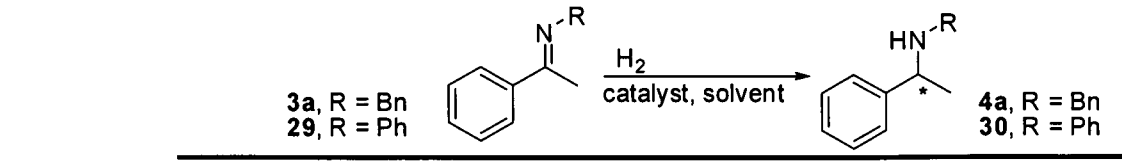


Scheme 1-16. Chiral cationic iridium complexes with P, N ligand.

Subsequently, they explored cationic iridium catalysts for imine hydrogenation in supercritical carbon dioxide ($scCO_2$) (Table 1-8). A catalyst **20b** with increased solubility in $scCO_2$ was synthesized by introduction perfluoroalkyl groups in the ligand

and anion (Scheme 1-16).[77]

Table 1-8. Enantioselective hydrogenation of acyclic imines with cationic Ir complexes



3a, R = Bn
29, R = Ph

4a, R = Bn
30, R = Ph

entry	substrate	catalyst	S/C	conv. (%)	ee (%)	config.	ref
1	**3a**	**20a**	25	100	76	*R*	76
2	**29**	**20a**	27	100	71[a]	*R*	76
3	**29**	**20a**	1000	99	86[b]	*R*	76
4	**29**	**20b**	1000	100	80	*R*	77
5	**3a**	**20b**	333	28.9	n.d.	/	77
6	**29**	**21**	1000	99	86[c]	*R*	78
7	**3a**	**22a**	200	63	98	*R*	79
8	**29**	**22a**	200	98	90	*R*	79
9	**29**	**22b**	200	99	92	*R*	80
10	**3a**	**23**	100	44	11	(+)	81
11	**29**	**23**	100	100	51	(-)	81
12	**3a**	**24**	25	97	63	*S*	82
13	**3a**	**25a**	50	100	81	*S*	83
14	**29**	**25b**	50	100	90	*S*	83
15	**29**	**26**	100	>99.5	93	*R*	84
16	**29**	**27**	100	>99.5	84	*R*	85
17	**3a**	(*S*,*S*)-**28b**	100	>99	91	*S*	86
18	**29**	(*R*,*S*)-**28a**	100	>99	91	*R*	86

[a] [**29**] = 0.22 M; [b] [**29**] = 0.035 M; [c] [**29**] = 0.03 M.

They found that the anion BARF dramatically affected the enantioselectivity of the

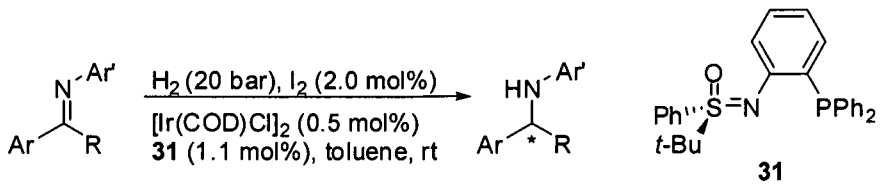
hydrogenation. The use of $scCO_2$ instead of CH_2Cl_2 allowed the catalyst loading to be lowered significantly, owing to a change in the rate profile of the reaction. Utilizing the selective extractive properties of $scCO_2$, the product could be readily separated from the catalyst, which could be recycled several times without significant loss of activity and enantioselectivity. Apart from Pfaltz's work, several groups also developed chiral cationic iridium complexes containing P, N ligands for acyclic imines hydrogenation (Scheme 1-16). Cozzi and coworkers developed a cationic heterocyclic phosphinooxazoline iridium complex **21** and its analogues for hydrogenation of imine **29**, affording the corresponding amine with 86% ee and full conversion (entry 6).[78] Andersson et al reported a range of new cationic phosphine-oxazoline iridium complexs **22a**, **22b** and their analogues for acyclic aromatic *N*-arylimines hydrogenation (Scheme 1-16).[79,80]

Afterward, Claver,[81] James,[82] Agbossou-Niedercorn,[83] Zhou,[84] Knochel[85] and Ding[86] reported similar chiral cationic iridium complexs **23**, **24**, **25**, **26**, **27** and **28**, with all containing P, N ligands (Scheme 1-15). In particular, Ding and coworker developed the iridium catalyst **28a**, **28b** and their analogues containing chiral phosphine-oxazoline ligand based on the spiro [4,4]-1,6-nonadiene backbone, which showed good activity and enantioselectivity for a wider scope of aliphatic and aromatic *N*-aryl and *N*-alkyl imines (Table 1-8, entries 17 and 18).[86]

Recently, Bolm and coworkers reported a neutral iridium complex containing a new C_1-symmetric sulfoximine for acyclic imine hydrogenation.[87] A series of phosphine-substitited sulfoximine ligands were synthesized and explored for the imine

hydrogenation. They found that the complex Ir-**31** showed excellent activities and enantioselectivities for a range of aromatic *N*-aryl imines in the presence of 2.0 mol% iodide additive. A series of protected aryl methyl, aryl ethyl and tetralone amines were obtained in 75-98% ee and full conversion (Table 1-9).[87]

Table 1-9. Enantioselective hydrogenation of acyclic imines with catalyst Ir-**31**



31

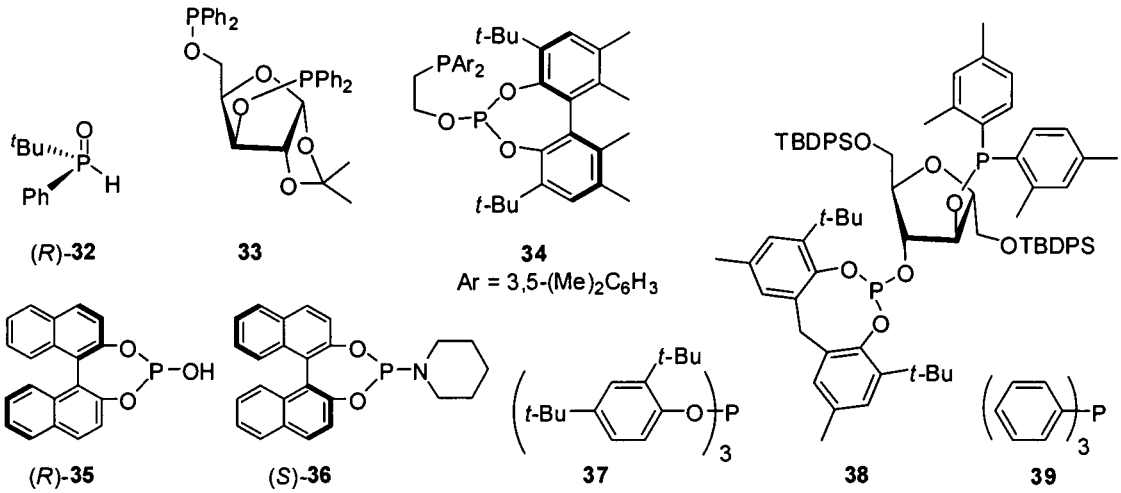
entry	Ar	Ar'	R	conv.	ee (%)	config.
1	Ph	4-MeO-C_6H_4	Me	full	96	(-)
2	Ph	4-MeO-C_6H_4	Et	full	92	(-)
3	2-Me-C_6H_4	4-MeO-C_6H_4	Me	full	94	(+)
4	2-Tetralone [a]	4-MeO-C_6H_4	/	full	91	(-)

[a] 2-Tetralone-derived imine.

Phosphite Ligands

de Vries and coworkers reported the first example of iridum complex bearing chiral monodenate phosphine oxide ligands for enantioselective hydrogenation of acyclic imines (Scheme 1-17).[88] A neutral complex, Ir-**32**, combined with pyridine showed good enantioslectivity for the model imine **3a** hydrogenation, the corresponding amine being obtained in 78% ee (Table 1-10, entry 1).[88] An improved 82% ee of the amine was obtained when lowering the reaction temperature to 0 °C (entry 2). However, the catalyst Ir-**32** showed no enantioselectivity for hydrogenation of imine **29** (entry 3). Pizzano and coworker reported a chiral phosphine-phosphite ligand **34** and its

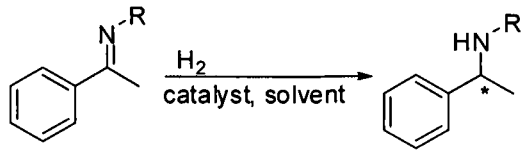
analogues for exploring hydrogenation of imine **29** (Scheme 1-17).[89] The imine was hydrogenated in 84% ee by using an Ir-**34** complex (entry 4).[89]



Scheme 1-17. Phosphite and phosphine ligands.

Recently, Reetz and Bondarev reported a combinatorial strategy to form numerous catalysts by homo-combination of the monodenate phosphite **35** with itself or hetero-combination of **35** with achiral phosphites or phosphines.[90] They found that the hetero-combination catalysts generally were more efficient than homo-combination catalyst by varying the ratio of chiral to achiral ligands (entries 5-8).[90] **3a** was hydrogenated to the corresponding amine with 88% ee when the catalyst was formed from $[Ir(COD)Cl]_2$, **35** and **39** in a ratio of 1:1.5:0.5 (entry 8).[90] Chiral phosphite iridium complexes were also explored for acyclic imines hydrogenation. Claver and coworkers developed a catalytic system by using a chiral cationic Ir-**33** complex with the ligand derived from xylose suger.[91] The catalyst showed moderate enantioselectivity for imine **29** hydrogenation (entry 9).

Table 1-10. Enantioselective hydrogenation of acyclic imines catalyzed by Ir-phosphite complexes



3a, R = Bn
29, R = Ph

4a, R = Bn
30, R = Ph

entry	substrate	catalyst	S/C	conv. (%)	ee (%)	ref
1	**3a**	$[Ir(COD)Cl]_2$+ **32** + Py	20	100	78[a] *S*	88
2	**3a**	$[Ir(COD)Cl]_2$+ **32** + Py	20	75	82 [a,b] *S*	88
3	**29**	$[Ir(COD)Cl]_2$+ **32** + Py	20	100	0[a]	88
4	**29**	$[Ir(COD)Cl]_2$+ **34**	100	full	84 *S*	89
5	**3a**	$[Ir(COD)Cl]_2$+ **35** + **37**	100	100	43[c] *S*	90
6	**3a**	$[Ir(COD)Cl]_2$+ **35** + **37**	100	100	80[d] *S*	90
7	**3a**	$[Ir(COD)Cl]_2$+ **35** + **39**	100	100	60[e] *S*	90
8	**3a**	$[Ir(COD)Cl]_2$+ **35** + **39**	100	100	88[f] *S*	90
9	**29**	$[Ir(COD)(\mathbf{33})]BF_4$	100	83	57 *S*	91
10	**3a**	$[Ir(COD)_2]BF_4$ + **38**	100	85	73 (-)	92
11	**29**	$[Ir(COD)_2]BArF$ + **36**	100	full	87 *R*	93

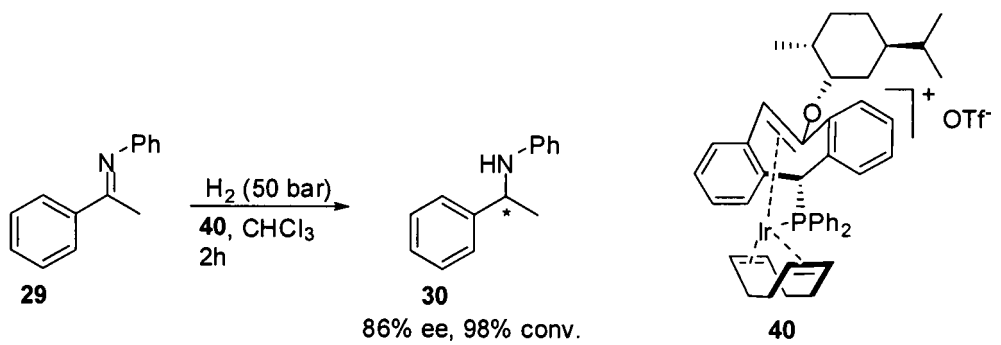
[a] $[Ir(COD)Cl]_2$+ **32** + Py = 1:2:2; [b]Temperature = 0 °C; [c] $[Ir(COD)Cl]_2$: **35** : **37** = 1:1:2; [d] $[Ir(COD)Cl]_2$: **35** : **37** = 1:2:2; [e] $[Ir(COD)Cl]_2$: **35** : **39** = 1:1:1; [f] $[Ir(COD)Cl]_2$: **35** : **39** = 1:1.5:0.5.

Subsequently, Castillon and co-workers developed a chiral diphosphite ligand **38** derived from the suger D-glucosamine (Scheme 1-17).[92] The Ir-**38** catalyst showed good activity and enantioselectivity for the model imine **3a** reduction, with the corresponding amine obtained in 73% ee (entry 10).[92] More recently, Minnarard, Feringa and de Vries et al developed an efficient hydrogenation by using an Ir-**36** complex bearing the BARF anion as catalyst.[93]

The bulky noncoordinating BARF was found to be beneficial for enantioselectivity. The catalytic system was sensitive to coordinating solvents and hydrogen pressure (entry 11).[93]

Olefin Ligands

Grutzmacher and coworkers reported the first example of chiral olefins as steering ligands in catalytic enantioselective hydrogenation of imines (Scheme 1-18).[94] The chiral complex **40** was prepared from $[Ir(COD)_2]OTf$ and the chiral olefin phosphane ligand. Catalyzed by prepared catalyst **40**, imine **29** was hydrogenated to the corresponding amine in 86% ee and 98% yield.[94] The results suggest that chiral olefins could be used as ligands for asymmetric hydrogenation.

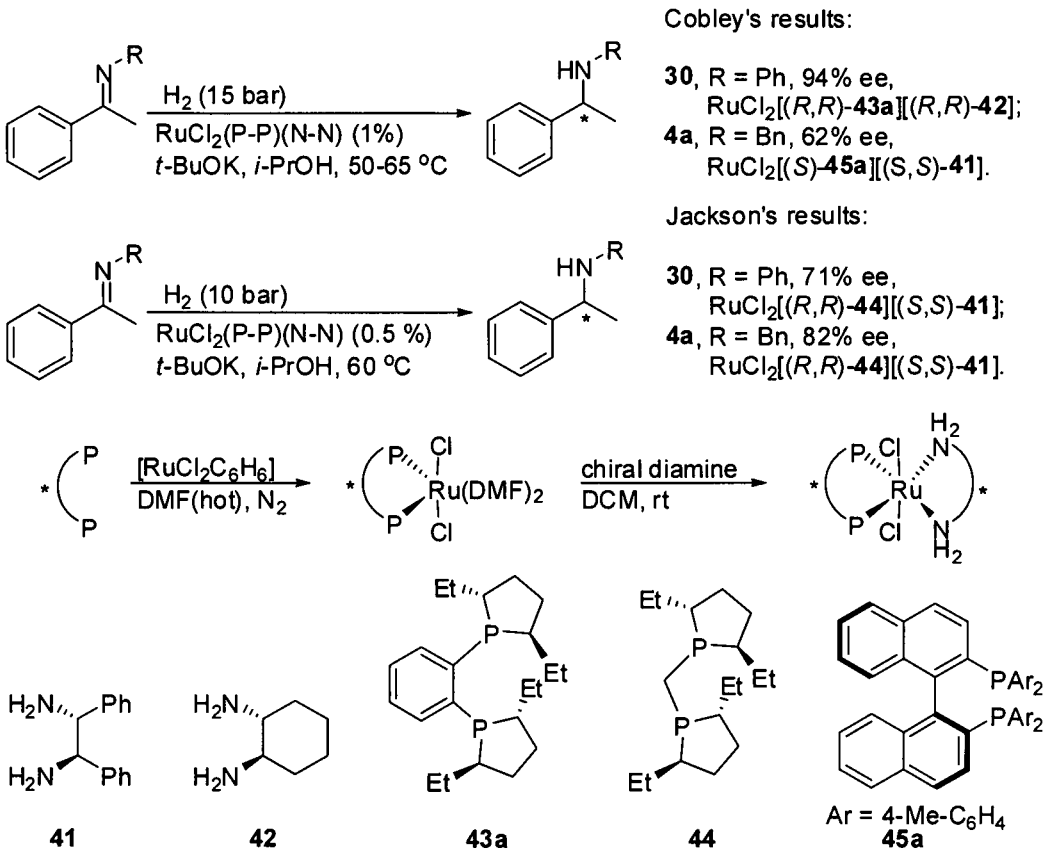


Scheme 1-18. Asymmetric hydrogenation of **29** with catalyst **40**.

2.2.4 Asymmetric Hydrogenation of Acyclic Imines with Ru Catalysts

Chiral ruthenium complexes are also recognized as an effective catalyst for asymmetric hydrogenation of imines.[6] So far, two types of chiral ruthenium complexs have been reported. Cobley and co-workers reported the use of $RuCl_2$(diphosphine)(diamine) for several cyclic and acyclic imines hydrogenation,

which is a well known catalyst for ketones hydrogenation (Scheme 1-19).[6,95]

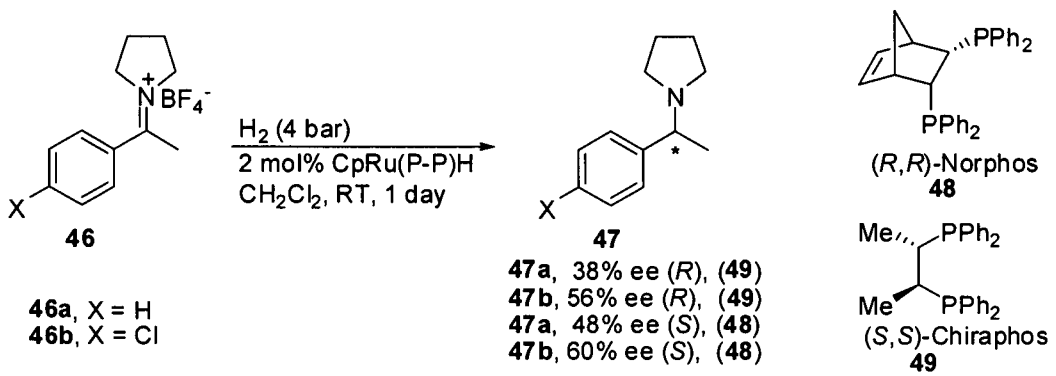


Scheme 1-19. Asymmetric hydrogenation of imines with Ru catalysts.

The catalyst was generally prepared under inert conditions by treatment of $[RuCl_2(benzene)]_2$ with a chiral diphosphine in hot DMF to produce the intermediate $RuCl_2(diphosphine)(DMF)_2$, and then the intermediate was reacted with a chiral diamine at room temperature to replace DMF, yielding easy to handle, stable precatalyst.[95] A library of chiral ruthenium complexes bearing different chiral diphosphines and chiral diamines were investigated for hydrogenation of acyclic imines. Imine **3a** and **29** were hydrogenated in 94% ee and 62% ee by using $RuCl_2$[(*R*,*R*)-**43a**][(*R*,*R*)-**42**] and $RuCl_2$[(*S*)-**45a**][(S,*S*)-**41**] with excess *t*-BuOK,

respectively.[95]

Recently, Jackson and coworkers explored similar catalysts system for imine hydrogenation by using the ligand **44** in combination with (*S*,S)-**41** and excess *t*-BuOK (Scheme 1-19).[96] Compared to Cobley's results, a lower ee of **30** was obtained, but the ee of **4a** was slightly higher. The results indicate that ruthenium complexes bearing various combinations of chiral diphosphine/diamine are needed in order to obtain a higher enantioselectivity for diverse substrates.



46

46a, X = H
46b, X = Cl

47

47a, 38% ee (*R*), (**49**)
47b, 56% ee (*R*), (**49**)
47a, 48% ee (*S*), (**48**)
47b, 60% ee (*S*), (**48**)

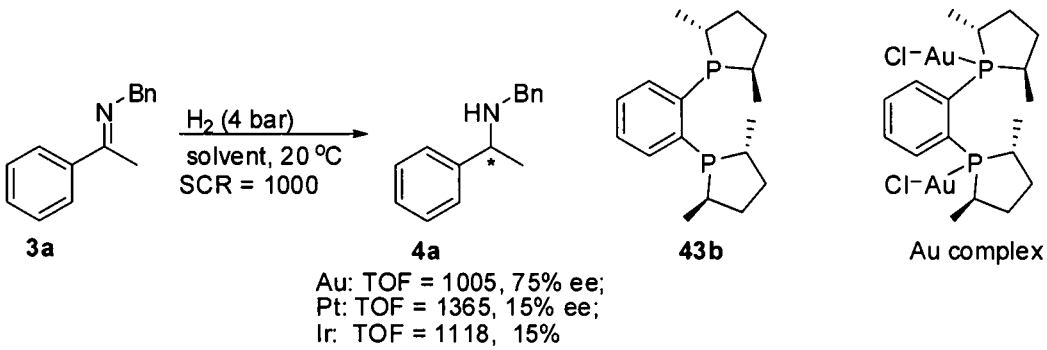
Scheme 1-20. Norton's asymmetric hydrogenation.

Different to $RuCl_2$(diphosphine)(diamine), a catalytic system operating via an ionic pathway was developed and the detail of mechanism was studied by Norton and coworkers (Scheme 1-20).[97,98] The prepared Ru-H hydride directly transfered the hydride from the metal to the iminium salt and catalyzed the reduction. Chiral amines **47a** and **47b** were obtained in 48% ee and 60% ee by using CpRu[(*R*,*R*)-**48**]H.[97,98] More detailed mechanism will be described in the Section 2.5.

2.2.5 Asymmetric Hydrogenation of Acyclic Imines with Au Catalyst

Gold complexs as catalysts have shown high activities for the formation of C-C,

C-O, C-N and C-S bonds.[99] Recently, Corma et al reported the first example of a chiral dinuclear gold complex-catalyzed asymmetric hydrogenation of **3a** (Scheme 1-21).[58] Bearing the same ligand **43b**, gold, platinum and iridium complexes were compared for the reduction. The results show that the chiral gold complex gave the highest enantioselectivity and a similar catalytic activity, which are comparable with those of the platinum and iridium complexes at the same conditions.[58] Up to now, this is the only example of gold-catalyzed asymmetric hydrogenation of imines. A more wide application of gold catalyzed asymmetric hydrogenation could be expected.



Scheme 1-21. Asymmetric hydrogenation of **3a** with [Au] catalyst.

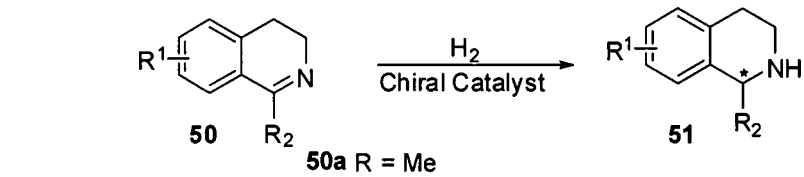
2.2.6 Asymmetric Hydrogenation of Cyclic Imines

Chiral cyclic amines can show high biological activities.[16,23] Especially, tetrahydroisoquinoline, tetrahydro-β-carboline and indoline widely exist in natural product synthesis and pharmaceutical products.[23] Buchwald's titanocene catalyst showed high selectivies for cyclic imine hydrogenation; however, their catalyst was difficult to handle.[51-53]

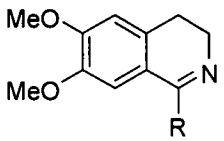
Several chiral Ir and Ru complexs associated with chiral phosphorus ligands were

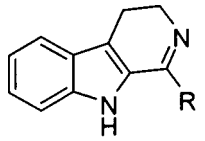
explored for the hydrogenation of cyclic imines to tetrahydroisoquinoline and tetrahydro-β-carboline with moderate to good ee's, but they generally have limited substrate scope (Table 1-11). Achiwa and Morimoto reported the synthesis of tetrahydroisoquinoline and tetrahydro-β-carboline by using an Ir-**5b** complex and it's analogues.[100] A range of Ir-complexs were screened for cyclic imines **50a**, **50i** and **50j**. The best ee's for **51a**, **51i** and **51j** were 28% ee, 30% ee and 20% ee by using Ir-**5b** with Bu_4NI, Ir-**52** with BiI_3 and Ir-**52** with Bu_4NI, respectively (entries 1-3).[100] Immediately afterwards, an improved enantioselectivity was obtained by using Ir-**52** with phthalimide as a co-catalyst. Cyclic imines **50a** and **50b** were hydrogenated to the corresponding tetrahydroisoquinoline **51a** and **51b** in 93% ee and 79% ee, respectively (entries 4 and 5).[101] Subsequently, Achiwa and coworkers employed their catalyst to the hydrogenation of **50g** to give tetrahydroisoquinoline **51g**, which is a precursor to alkaloid calycotomine; the benzyl group can be easily removed by Pd-catalyzed hydrogenation. Compounds **51g** and **51h** were obtained in 86% ee and 89% ee by using an Ir-**45b** complex with F4-phthalimide and parabanic acid as additive (entries 6 and 7).[102] Similarly **51c**, **51d**, **51e** and **51f** were obtained in 31%-88% ee by using Ir-diphosphine complexes in the presence of co-catalyst phthalimide (entries 8-12).[103] $RuCl_2$(diphosphine)(diamine) is also efficient for hydrogenation of **50a**. Cobley and Jackson independly reported the hydrogenation of **50a**, obtaining 79% ee and 89% ee by using $RuCl_2$[(*R*,*R*)-**43a**][(*R*,*R*)-**42**] and $RuCl_2$[(*R*,*R*)-**53**][(*S*,*S*)-**41**] as catalyst, respectively (entries 13 and 14).[95,96]

Table 1-11. Enantioselective hydrogenation of cyclic imines to tetrahydroisoquinoline and tetrahydro-β-carboline



50a R = Me
50b R = Et
50c R = 3,4-$(MeO)_2C_6H_3$
50d R = 3,4-$(MeO)_2C_6H_3CH_2$
50e R = 3,4-$(MeO)_2C_6H_3CH_2CH_2$
50f R = (*E*)-3,4-$(MeO)_2C_6H_3CH$=CH
50g R = $BnOCH_2$
50h R = $BnOCH_2CH_2CH_2$

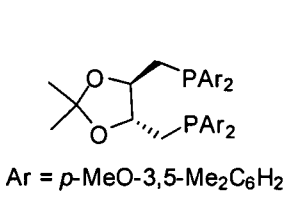




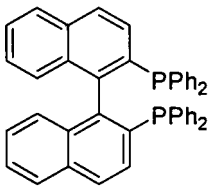
50i R = Me
50j R = Et

entry	imine	Ir(I)-ligand	cocatalyst	conv. (%)	ee (%)	ref
1	**50a**	**5b**	Bu_4NI	91	28(*S*)	100
2	**50i**	**52**	BiI_3	97	30 (*R*)	100
3	**50j**	**52**	Bu_4NI	100	20 (*R*)	100
4	**50a**	**52**	phthalimide	95	93 (*S*)	101
5	**50b**	**52**	phthalimide	/	79 (*S*)	101
6	**50g**	(*R*)-**45b**	F_4-phthalimide	85	86 (*S*)	102
7	**50h**	(*S*)- **45b**	parabanic acid	99	89 (*S*)	102
8	**50c**	(*S*)-**45b**	phthalimide	50	31(*R*)	103
9	**50d**	**52**	F_4-phthalimide	84	88 (*S*)	103
10	**50e**	**52**	phthalimide	75	87 (*S*)	103
11	**50e**	(*S*)-**45b**	phthalimide	89	82 (*S*)	103
12	**50f**	**52**	phthalimide	85	86 (*S*)	103
13	**50a**	catalyst[a]	none	80	79	95
14	**50a**	catalyst[b]	none	100	89	96

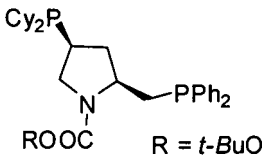
[a] $RuCl_2$[(*R*,*R*)-**43a**][(*R*,*R*)-**42**] as catalyst; [b] $RuCl_2$[(*R*,*R*)-**53**][(*S*,*S*)-**41**] as catalyst.



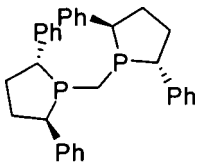
(4*R*, 5*R*)-MOD-DIOP
5b



BINAP
45b



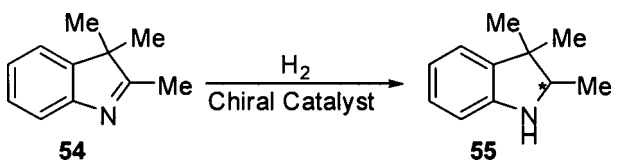
(2*S*,4*S*)-BCPM
52



(*R*,*R*)-Ph-BPM
53

Asymmetric hydrogenation of 2,3,3-trimethylindolenine **54** was investigated by using chiral iridium and ruthenium complexes (Table 1-12). Although the highest enantioselectivity for **55** was obtained by using chiral titanocene catalyst,[51-53] Ir-**8a**,[71] Ir-**5b**,[104] Ir-**56**[105] and $RuCl_2$[(*R*,*R*)-**57**][(*S*,*S*)-**58**][95] also showed good enantioselectivity (entries 1-4). When the reaction medium was ionic liquid, Ir-**52** also displayed good activity in the absence of phthalimide (entry 6).[106]

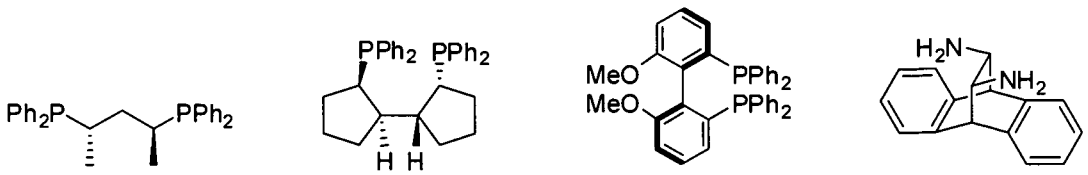
Table 1-12. Enantioselective hydrogenation of 2,3,3-trimethylindolenine **54**



54 **55**

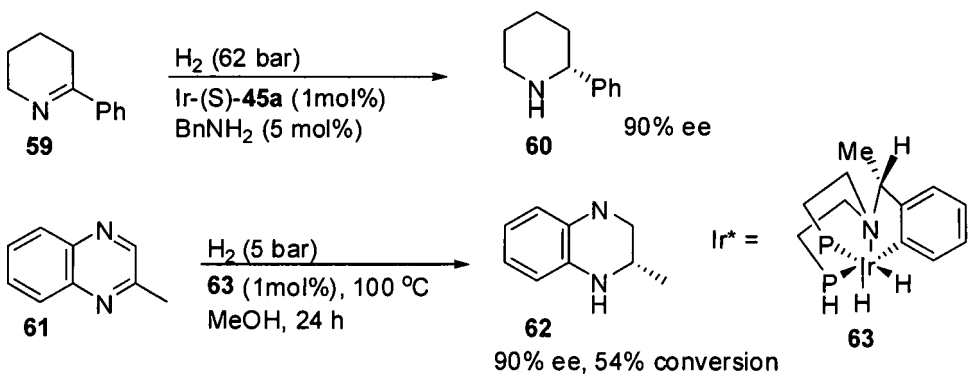
entry	catalyst	cocatalyst	conv. (%)	ee (%)	ref
1	[Ir(S,S)-**8a**)HI_2]	/	99	80 (+)	71
2	$[Ir(COD)Cl]_2$+ **5b**	Bu_4NI	99	81 (+)	104
3	$[Ir(COD)Cl]_2$+(*R*,*R*)-**56**	phthalimide	100	95 (+)	105
4	$RuCl_2$[(*R*,*R*)-**57**][(*S*,*S*)-**58**]	/	/	88	95
5[a]	$[Ir(COD)Cl]_2$+**52**	/	98	84	106

[a] $[C_{10}mim][BF_4]$ as solvent



(*S*,*S*)- BDPP **8a** | (*R*,*R*)-BICP **56** | (*R*)-MeO-BIPHEP **57** | ANDEN **58**

Cyclic imine **59** was hydrogenated to the corresponding amine **60** with up to 90% ee by using chiral Ir-**45a** in the presence of a protic amine, benzylamine (Scheme 1-22).[107] 2-Methyl-1,2,3,4-tetrahydroquinoxaline **62** was obtained in 90% ee and 54% conversion by a preformed orthometallated Ir dihydride complex **63** (Scheme 1-22).[76,77]

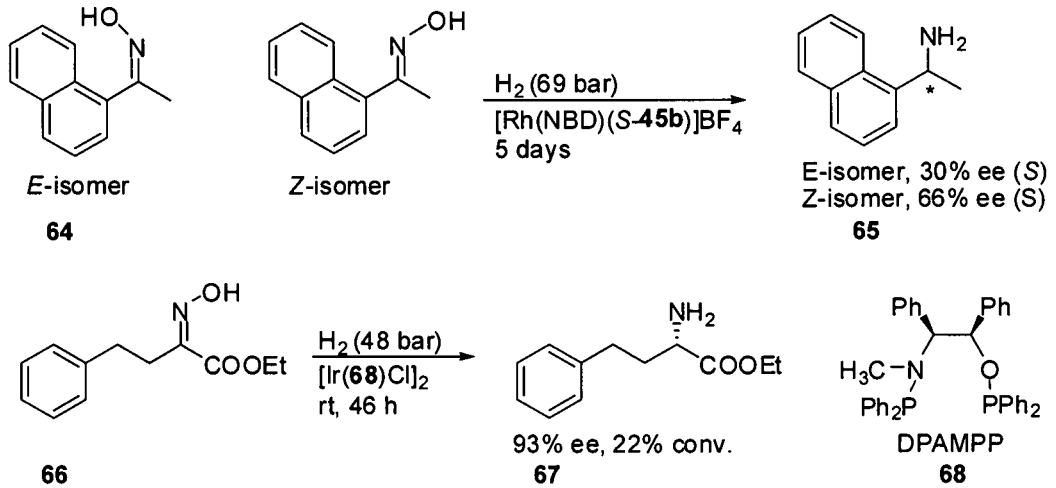


Scheme 1-22. Asymmetric hydrogenation of cyclic imines.

2.2.7 Asymmetric Hydrogenation of C=N-X Substrates

Isolated pure *E*, *Z*-isomer of 1-acetonphthone oxime **64** was hydrogenated to amine **65** in 30% ee and 66% ee by using a chiral cationic Rh-**45b** complex, respectively (Scheme 1-23).[108] This result suggests that the C=N bond isomerization markedly influences enantioselectivity in the hydrogenation of imines. Jiang and coworker reported the hydrogenation of ketone oximes by using a neutral catalyst Ir-**68** complex

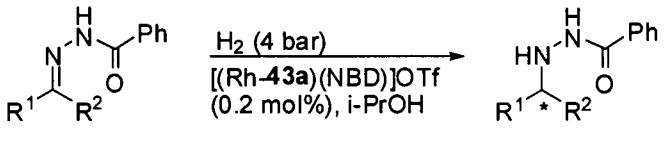
with iodide as an additive. Amino ester **67** was obtained in 93% ee and 22% conversion (Scheme 1-23).[109]

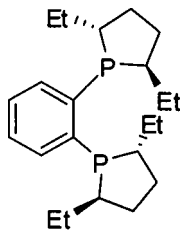


Scheme 1-23. Asymmetric hydrogenation of oximines.

Burk and co-workers developed an efficient catalytic system for the hydrogenation of *N*-acylhydrazone substrates by using a chirla cationic Rh-**43a** complex (Table 1-13).[110,111] In their investigation, they found low temperature (-10 °C to -15 °C) and a protic solvent isopropyl alcohol were more beneficial to improve enantioselectivity (entries 1-4).[110,111] Various *N*-acylhydrazones of aromatic ketone, alphatic ketone and keto ester were hydrogenated to form *N*-benzoylhydrazones in up to 97% ee (entries 5-7). Their catalytic system showed high selectivities for various functional groups, such as alkene, alkyne, ketone, aldehyde, imine and so on.[110,111] The resulting chiral products could be easily converted into free amines by treatment with samarium diiodide or converted into free amines by treatment with 3N HCl.[110,111] The carbonyl function of the hydrazones is crucial to achieve high selectivities and good activities.

Table 1-13. Enantioselective hydrogenation of *N*-acylhydrazone





43a

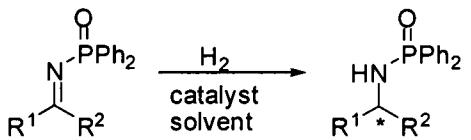
entry	R^1	R^2	temperature (°C)	time (h) [a]	ee (%)	config.
1	C_6H_5	Me	20	2	7 [b]	*S*
2	C_6H_5	Me	20	1	88	*S*
3	C_6H_5	Me	0	12	92	*S*
4	C_6H_5	Me	-10	24	95	*S*
5	4-$NO_2C_6H_4$	Me	0	12	97	*S*
6	Cy	Me	-15	36	72	*S*
7	CO_2Me	Et	0	36	91	*S*

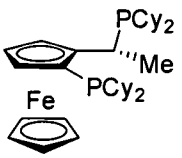
[a] Time allowed for complete conversion to product; [b] Toluene as solvent.

In 2001, Spinder and Blaser reported the asymmetric hydrogenation of *N*-diphenylphosphinyl ketimines by using a cationic catalyst Rh-**16b** in situ prepared from $[Rh(NBD)_2]BF_4$ and ligand **16b**.[112] Several *N*-diphenylphosphinyl ketimines were hydrogenated to the corresponding amines in 30% to 99% ee at 60 °C under 70 bar hydrogen pressure (Table 1-14, entries 1-3). The strong basicity of the ligand **16b** was important for the hydrogenation to achieve good reactivity and enantioselectivity, and, the enantioselectivities of product showed high sensitivity to ligand, metal and substrate structure.[112] Subsequently, hydrogenation of a wide scope of *N*-diphenylphosphinyl ketimines was successfully realized by using Pd-**69**

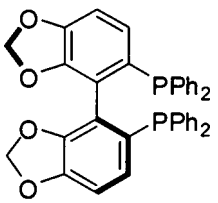
complex.[113,114] A range of *N*-diphenylphosphinyl ketimines of aromatic ketones were hydrogenated in 87%-99% ee at room temperature under 69 bar hydrogen pressure (Table 1-14, entries 4-7).[113,114] The products can be hydrolyzed to unracemized free amines in acidic conditions.

Table 1-14. Enantioselective hydrogenation of *N*-diphenylphosphinyl ketimines





16b



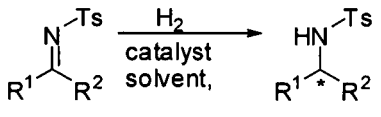
69

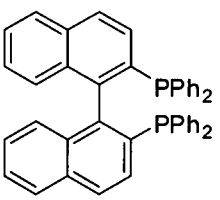
entry	R^1	R^2	catalyst	conv (%)	ee (%)	config.
1	C_6H_5	Me	Rh-**16b**	100	99	*R*
2	4-CF_3-C_6H_4	Me	Rh-**16b**	98	95	*R*
3	4-Cl-C_6H_4	Me	Rh-**16b**	53	30	*R*
4	C_6H_5	Me	Pd-**69**	>95	96	*S*
5	4-Cl-C_6H_4	Me	Pd-**69**	94	94	*S*
6	C_6H_5	Et	Pd-**69**	95	87	*S*
7	2-Furyl	Me	Pd-**69**	62	87	*S*

Asymmetric hydrogenation of *N*-tosylimines was earliest realized by using a Ru-**45b** catalyst.[115] Good ee's were obtained in the presence of 5% preformed catalyst at 40 °C under 72 bar hydrogen pressure in THF (Table 1-15, entries 1 and 2).[115] However, the catalytic system showed low reactivity and enantioselectivity for *N*-tosylamines derived from alphatic ketones. The chiral cationic Pd-**70** complex showed excellent enantioselectivity for hydrogenation of *N*-tosylamines (entries 3-5).[57,114] A range of *N*-tosylimines of aromatic ketones and alphatic ketones were hydrogenated to

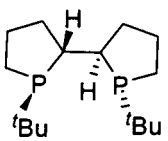
N-tosylamines in up to 99% ee at 40 °C under 77 bar hydrogen pressure (entries 3-5).[57] Subsequently, Zhou et al reported a cationic Pd-**71** catalyzed hydrogenation of *N*-tosylamines, obtaining excellent results as well (entries 6 and 7).[114] Notwithstanding these excellent results, the high pressure and catalyst loading and the difficulty to remove the protect group are still problems for this type imine hydrogenation.

Table 1-15. Enantioselective hydrogenation of *N*-tosylimines

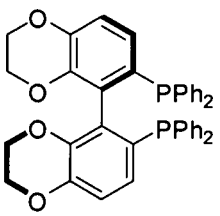




45b



70



71

entry	R^1	R^2	catalyst	conv. (%)	ee (%)	config.
1	Ph	Me	Ru-(*R*)-**45b**	82 [a]	62	*R*
2	2-tetralon	/	Ru-(*R*)-**45b**	77 [a]	82	*R*
3	Ph	Me	Pd-**70**	>99	99	*R*
4	1-naphthyl	Me	Pd-**70**	>99	99	(-)
5	*t*-Bu	Me	Pd-**70**	>99	98	*R*
6	Ph	Me	Pd-**71**	84	96	*S*
7	*t*-Bu	Me	Pd-**71**	94	91	*S*

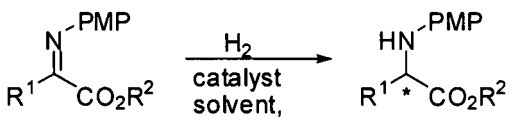
[a] isolated yield

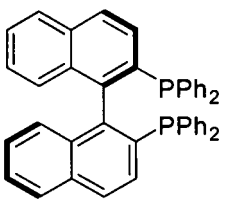
2.2.8 Asymmetric Hydrogenation of Imino Esters

Enantioselective hydrogenation of fluorinated α-imino esters was successfully realized by using a chiral cationic Pd-**45b** complex.[116] The less coordinating solvent

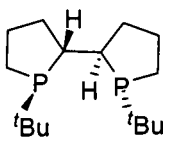
2,2,2-trifluoroethanol (TFE) dramatically improved the reactivities and enantioselectivities in the hydrogenation of α-imino esters.[116] A series of α-imino esters were hydrogenated to form α-fluorinated amino esters with ee values ranging from 30% to 91% at room temperature under 103 bar hydrogen presure (Table 1-16, entries 1-4).

Table 1-16. Enantioselective hydrogenation of α-imino esters





(*R*)-**45b**



70

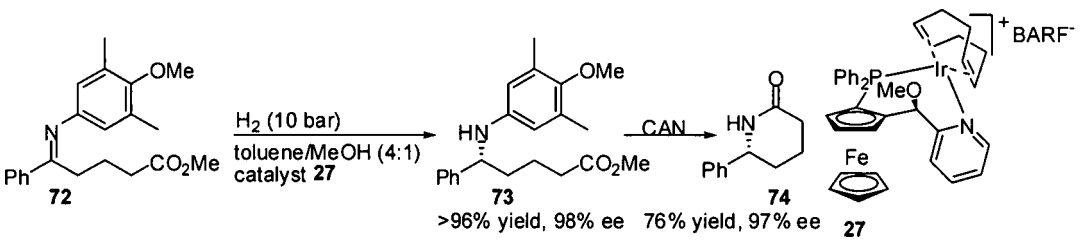
entry	R^1	R^2	catalyst	conv. (%)	ee (%)	config.
1	CF_3	Et	Pd-**45b**	99	88 [a]	*R*
2	$CClF_2$	*t*-Bu	Pd-**45b**	69	81	*R*
3	C_7F_{15}	Bn	Pd-**45b**	98	61	*R*
4	CHF_2	Bn	Pd-**45b**	75	30	*R*
5	Ph	CH_3	Rh-**70**	>99	95	*S*
6	4-Br-Ph	CH_3	Rh-**70**	>95	92	(-)
7	2-MeO-Ph	CH_3	Rh-**70**	>95	95	(-)
8	2-naphthyl	CH_3	Rh-**70**	>95	90	(-)
9	cyclohexyl	CH_3	Rh-**70**	84	94	(+)

[a] 91% ee was obtained, when 5 equiv of n-Bu_4NHSO_4 was added.

It was suggested that TFE coordinated weakly to palladium and thus was replaced by less coordinative fluorinated imines. TFE could also affect the imino group by

protonation or hydrogen bonding.[116] Recently, Zhang and coworkers reported a new catalytic system based on a cationic rhodium complex bearing diphosphine ligand **70** for the hydrogenation of α-imino esters.[117] A range of α-imino esters were hydrogenated to form glycine with excellent ee values ranging form 91% to 95% (entries 5-9).[117]

Knochel and co-worker reported an enentioselective protocol to synthesise chiral lactam **74** via asymmetric hydrogenation of imine **72** bearing a remote ester group followed by deprotection by using CAN. The protected amino ester was obtained in 98% ee and 96% yield by using the complex **27** at room temperature under 10 bar hydrogen pressure (Scheme 1-24).[85]



Scheme 1-24. Asymmetric hydrogenation of imino esters.

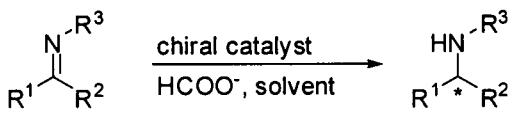
2.2.9 Asymmetric Transfer Hydrogenation of Imines with Metal Catalysts

Asymmetric transfer hydrogenation is one of the most common and direct methods to reduce C=O, C=C and C=N bonds. Other than hydrogenation, transfer hydrogenation generally employs hydrogen donor as hydrogen source, such as formate salt, IPA or Hantzsch ester.[118] In catalytic transfer hydrogenation, the hydrogen source

is normally transferred into a byproduct which could affect the activity and enantioselectivity of catalyst.[119] However, catalytic transfer hydrogenation is still a good choice for industrial processes and academic research, because of its operational simplicity and versatility.

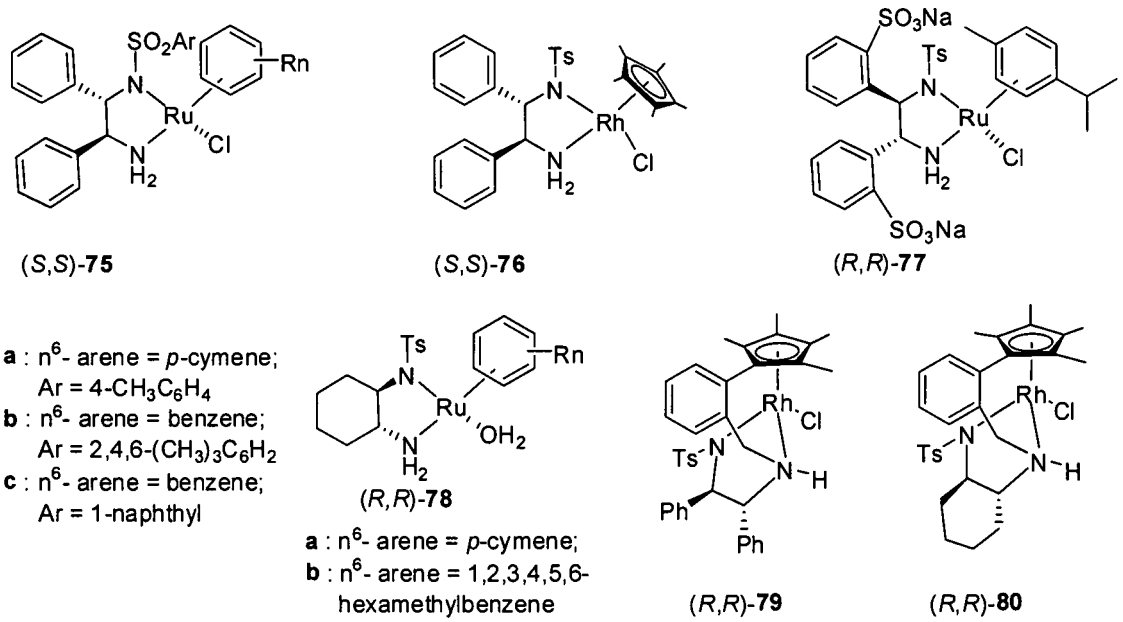
Compared to asymmetric hydrogenation of imines, only a few cases of metal-catalyzed transfer hydrogenation of acyclic and cyclic imines have been successfully realized.[2,6,8,118,120] Table 1-17 summarises the major results.

Table 1-17. Transfer hydrogenation of imines with diamine ligated-metal catalysts



entry	imine	catalyst	time (h)	yield (%)	ee (%)	config.	ref
1 [a]	**3a**	(*S*,*S*)-**75b**	36	72	77	*S*	50
2 [a]	**50a**	(*S*,*S*)-**75a**	3	>99	95	*R*	50
3 [a]	**50c**	(*S*,*S*)-**75c**	8	>99	84	*R*	50
4 [a]	**50i**	(*S*,*S*)-**75c**	5	86	97	*R*	50
5 [a]	**3a**	(*S*,*S*)-**76**	10 min	88	8.4	*S*	121
6 [a]	**50a**	(*S*,*S*)-**76**	10 min	96	89	*R*	121
7 [b]	**50c**	(*S*,*S*)-**76**	3	89	3.2	*R*	121
8 [b]	**50a**	(*R*,*R*)-**77**	10	97	95	*S*	122
9 [b]	**50b**	(*R*,*R*)-**77**	25	68	92	*S*	122
10 [b]	**50i**	(*R*,*R*)-**77**	8	97	99	*S*	122
11 [b]	**3a**	(*R*,*R*)-**78b**	2	(100)	91	/	123
12 [b]	**50a**	(*R*,*R*)-**78a**	2	(100)	88	/	123
13 [a]	**3a**	(*R*,*R*)-**80**	15 min	70 (100)	44	*S*	124
14 [a]	**50a**	(*R*,*R*)-**79**	15 min	72 (100)	87	*S*	124
15 [a]	**50i**	(*R*,*R*)-**79**	15 min	69 (100)	88	*S*	124

[a] S/C = 200; [b] S/C =100; [c] Conversion is state in parentheses.



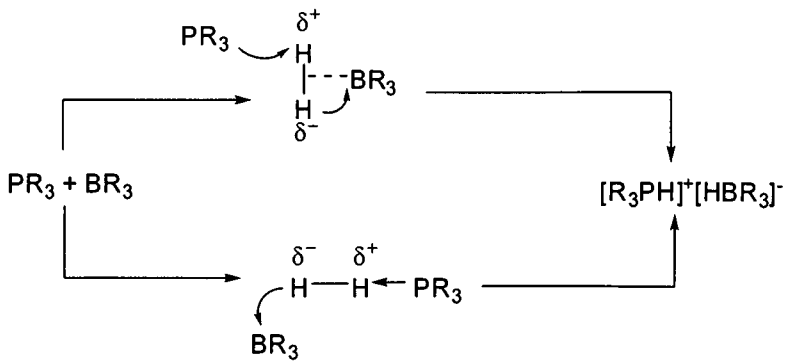
Scheme 1-25. Diamine-ligated catalysts for asymmetric transfer hydrogenation.

Noyori and coworkers demonstrated the first enantioselective transfer hydrogenation of imines by using diamine ligated chiral Ru(II) complexes (*S*,*S*)-**75** in the azeotropic mixture of formic acid and triethylamine (HCOOH: Et_3N = 5:2) (Scheme 1-25).[50] Cyclic imines **50a** and **50i** were reduced to tetrahydroisoquinoline **51a** with 95% ee and tetrahydro-β-carboline **51i** with 97% ee (entries 2 and 4), respectively. However, replacing the substituent group methyl with aryl, **50c** was completely reduced to produce **51c**, but with a lower ee value of 84% in a prolonged time of 8 h (entry 3). Furthermore, the activity of catalyst was significantly lowered when the diamine ligated catalyst **75** encountered acyclic imine **3a** (entry 1).The catalyst **76** showed higher activity for the reduction of cyclic and acyclic imines, but lower enantioselectivity for acyclic imine **3a** and aryl substituted imine **50c** (entries

5-7).[121] Recently, Deng and coworkers reported a catalytic transfer hydrogenation of cyclic imines and iminium salts in water by using the water-soluble Ru(II) complex **77** with CTAB as additive.[122] The catalyst show slightly higher enantioselectivity but lower activity for the reduction of cyclic imines (entries 8-10). The more electron rich catalyst **78** showed excellent enantioselectivity for acyclic imine reduction (entry 13),[123] and Will's tethered catalysts **79** and **80** showed high activity for cyclic and acyclic imines (entries 13-15).[124,125]

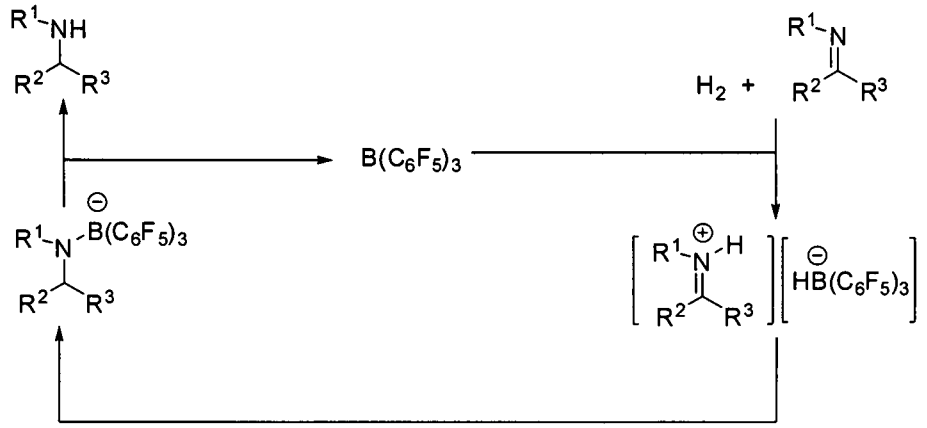
2.3 Metal-free Catalytic Asymmetric Hydrogenation

Recently, Stephan and coworkers found a new type of bulky Lewis acid-base pair consisting of borane $B(C_6F_5)_3$ and phosphine, which could catalyze hydrogenation of ketones, imines, nitriles and aziridines.[126-131] For dihydrogen cleavage, they suggested that the Lewis acid BR_3 interacted with H_2, resulting in polarization of H_2 and thus facilitating protonation of phosphine. Both the Lewis acid and base interacting with hydrogen are also possible in splitting hydrogen (Scheme 1-26).[129] Unsaturated substrates might be reduced by the resulting phosphonium borate salt.



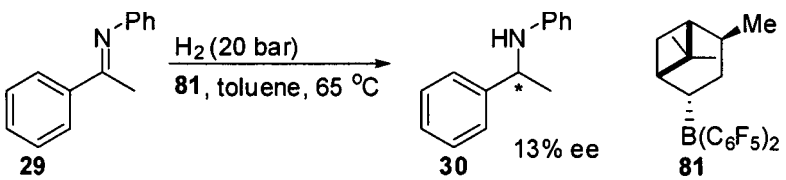
Scheme 1-26. Possible mechanism for heterolytic cleavage of H_2 by phosphine and borane.

Further studies by Stephan and coworkers showed that the combination of *N*-Lewis base and Lewis acid BR_3 could also split hydrogen (Scheme 1-27).[127,128] The Lewis acid $B(C_6F_5)_3$ and imine might form iminium hydridoborate ion pair under hydrogen pressure, which was confirmed by spectroscopy and X-ray crystal structure. The hydridoborate transfers the hydride to the protonated imine, and dissociation of BR_3 releases the amine product.



Scheme 1-27. Possible mechanism for catalytic hydrogenation of imine.

Based on this concept, Klankermayer and coworker employed a chiral (+)-α-pinene derived borane as a catalyst for acyclic imine enantioselective hydrogenation (Scheme 1-28).[128] Although only 13% ee was obtained, this is the first example of metal-free catalytic asymmetric hydrogenation of imines under mild conditions. This finding will encourage further extension of the use of chiral Lewis acid-base pairs asymmetric hydrogenation.



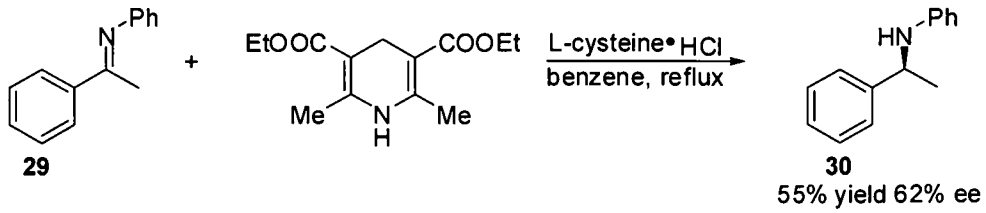
Scheme 1-28. Asymmetric hydrogenation of imine **29** with bulky Lewis acid-base pair.

2.4 Organocatalytic Asymmetric Transfer Hydrogenation

In the organometal-catalyzed enantioselective hydrogenation or transfer hydrogenation, transition-metal catalysts generally play two roles: enabling hydride transfer from a hydrogen source, such as molecular hydrogen, isopropyl alcohol or formate salt, to a unsaturated substrate, and chirality transfer from a chiral ligand to the prochiral substrate.[2,6,8,118] Owing to their high activity and enantioselectivity, various chiral transition metal catalysts have been applied to asymmetric reduction of olefins, ketones and C=N functions.[2,6,8] However, asymmetric organocatalysis has shown better enantioselectivity and wider scope in the reduction of C=N functional groups in many case.[119] In particular, chiral Brønsted acids as a catalyst and Hantzsch dihydropyridine as the hydrogen source have been combined for enentioselective reduction of C=C and C=N double bonds.[119]

2.4.1 Reduction of Imines

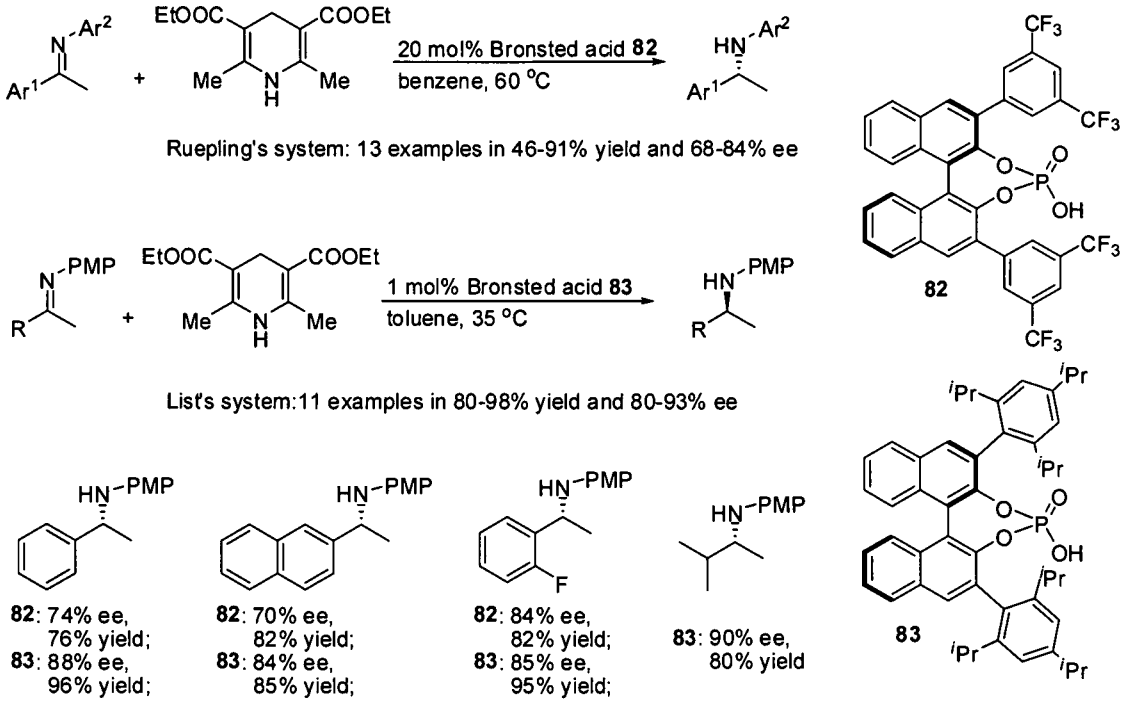
The earliest enantioselective organocatalytic reduction of imines was reported by Singh and Batra in 1989 (Scheme 1-29).[132] Chiral Brønsted acids and Hantzsch esters were selected for the reduction of *N*-phenyl ketimine **29** prepared from acetophenone and aniline. A range of chiral acids were examined for optimum conditions. One of the amino acids, cysteine was selected as an effective catalyst to reduce **29** to produce amine **30** in 55% yield and 62% ee.



29 **30**
55% yield 62% ee

Scheme 1-29. The earliest example of organocatalytic reduction of acyclic imines.

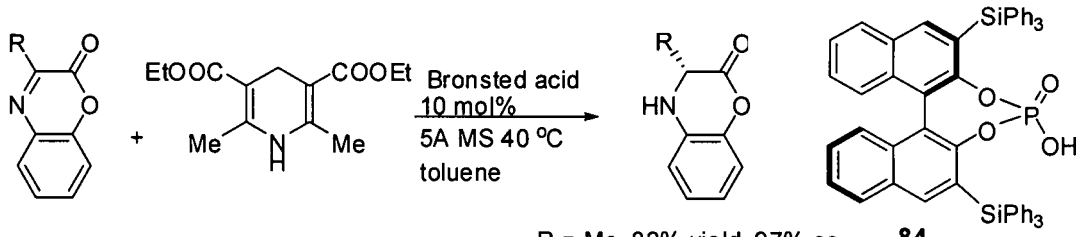
Although the first organocatalytic asymmetric reduction of imines afforded enantiomerically enriched amine, the transformation is of low productivity and enantioselectivity. Recently, Rueping and List's groups demonstrated an excellent, similar organocatalytic system for the reduction of acyclic imines by using different chiral phosphoric acids (Scheme 1-30).[133,134] The chiral phosphoric acid was derived from the Akiyama-Terada family of binol-derivatives.[135] In Rueping's catalytic sytem, electron withdrawing and bulkyl 3,5-(CF_3)-phenyl-substituted binaphthol phosphoric acid **82** (20%) was used for the reduction of acyclic imines in a low concentration (0.02 M) of substrate at 60 °C.[133] Thirteen enantiomerically enriched amines were obtained in 46-91% yield and 68-84% ee. A more bulky *ortho*-2,4,6-triisopropyl-phenyl substituted binaphthol phosphoric acid (TRIP) **83** was selected as the catalyst by List.[134] Higher levels of isolated yields and enantioslectivites were obtained by using 1% of **83** for the reduction of *N*-aryl ketimines.



Scheme 1-30. Organocatalytic reduction of imines with Brønsted acids.

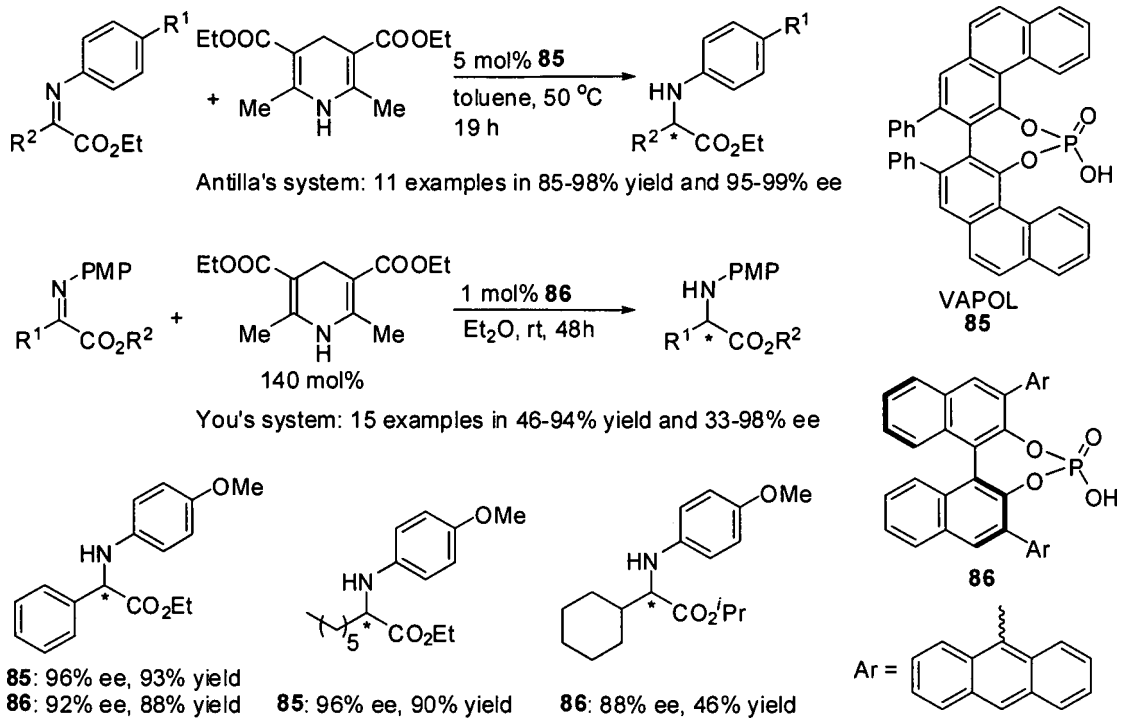
2.4.2 Reduction of Imino Esters

Following reduction of imines, enantioselective reduction of imino esters was also realized by using the chiral Akiyama-Terada family of Bronsted acids together with Hantzsch ester.[136-139] Two examples of reduction of cyclic imino ester are given in Scheme 1-31.[136] Methyl and ethyl substituted cyclic amino esters were obtained in 97% ee (82% yield) and 79% ee (27% yield) by using 10% of chiral phosphoric acid **84** at 40 °C in benzene. Owing to the terminal CH_3 of the ethyl group shielding the C=N *Si*-face which is exposed to hydride addition, lower activity and enantioselectivity were observed for reduction of ethyl imino ester.[136]



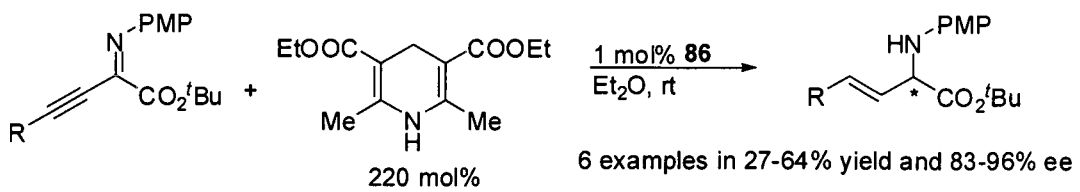
Scheme 1-31. Organocatalytic reduction of cyclic imino esters.

Subsequently, Antilla and You independently demonstrated a simliar organocatalytic reduction of α-imino ester by using chiral phosphoric acids and Hantzsch ester in nonpolar solvent (Scheme 1-32).[137,138] In Antilla's study, the vaulted biaryl phosphoric acid **85** showed high activity and enantioselectivity in transfer hydrogenation of α-imino esters in toluene at 50 °C. A range of aromatic and alphatic amino esters were obtained in 95-99% ee and 85-98% yield (Scheme 1-32). The ester group is found to significantly affect the activity and enantioselectivity.[138] Using **86** as catalyst, a range of α-imino esters were reduced to α-imino esters by You et al with 33-98% ee and 46-94% yield. However, higher levels of isolated yields and enantioslectivites were obtained by using 5% of **85** rather than 10% of **86** in the transfer hydrogenation of α-imino esters.



Scheme 1-32. Organocatalytic reduction of acyclic imino esters.

Shortly after, a further extension into β,γ-alknyl α-imino esters was explored by using the same acid **86** in You's research group.[139] Several *trans*-alkenyl α-amino esters were obtained in 83-96% ee and 27-64% yield by reduction of the C≡C triple bond followed by that of the C=N double bond (Scheme 1-33).



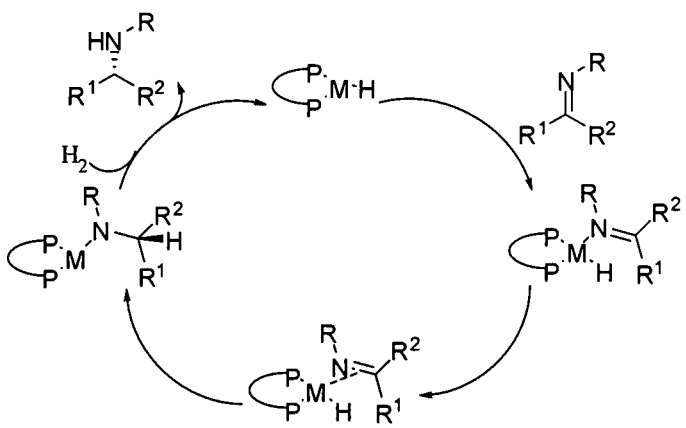
Scheme 1-33. Organocatalytic reduction of β,γ-alknyl α-imino esters.

2.5 Mechanistic Aspects of Asymmetric Hydrogenation

So far, only a few detailed studies of homogeneous hydrogenation of imines have

been reported. Based on those studies, two types of mechanism, classical and ionic pathways, were postulated for the transition metal-catalyzed hydrogenation of imines. In James' mechanistic investigation of Rh-catalyzed hydrogenation of imines, several intermediates involving imine coordination to the Rh centre via the nitrogen lone pair was isolated during the hydrogenation of the cyclic imine **50a**.[69] They suggested oxidative addition of hydrogen to rhodium (I) occurs after the imine is coordinated.

As described in Section 2.2.3, Osborn and Chan found that the isolated $[Ir(diphosphine)I_4]^-$, $[Ir(diphosphine)I_2]_2$, and $[Ir(diphosphine)I_3]_2$ showed good activity for hydrogenation of imines **13a**, **29**, and **54**.[71] A same active monomeric Ir-H species was suggested to form in the catalytic cycle regardless of which precatalyst was used. Based on their studies, a catalytic cycle for the iridium-catalyzed imine hydrogenation was postulated (Scheme 1-34).

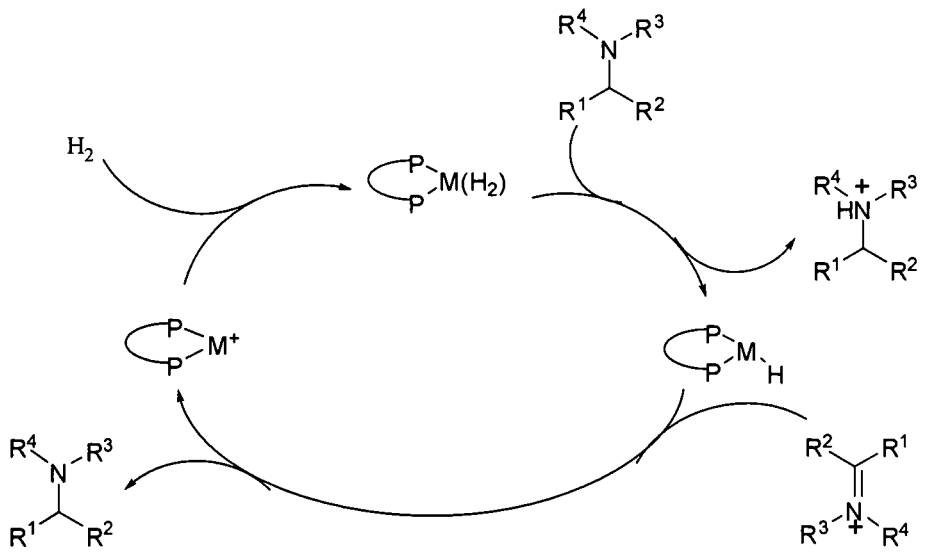


Scheme 1-34. Classical pathway for hydrogenation of imines with transition metal complex.

Firstly, the starting metal hydride (M-H) binds the imine via the lone pair in a η^1 manner. Following the first step, a η^1 to η^2 migration followed by insertion into the

M-H bond leads to an M-amine complex. The last step is hydrogenolysis of M-N bond to generate the chiral amine and the active catalyst. Buchwald proposed a similar mechanism for the Ti-catalyzed hydrogenation of imines.[53] However, the imine coordinates to the metal centre even if the first step is hydrogen activation.

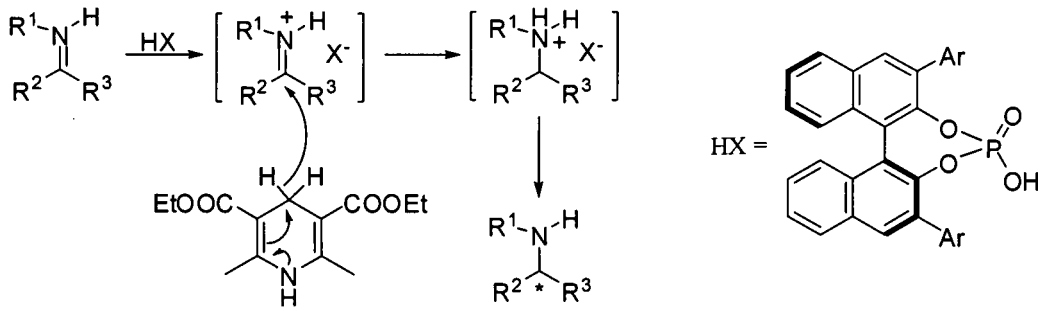
On the other hand, direct hydride transfer from M-H to unsaturated C=N double bond without imine coordination is possible. Norton and coworkers investigated the reaction mechanism of stoichiometric reduction of an iminium salt with CpRu(diphosphine)H to generate enantiomerically enriched amine.[97,98] High pressure NMR experiments show that the hydride transfer step is rate-determining. Based on their studies, an ionic mechanism for imine hydrogenation was assumed. The catalytic cycle is depicted in Scheme 1-35 below.



Scheme 1-35. Ionic pathway for hydrogenation of imines with the [CpRu(diphosphine)]H catalyst.

A similar ionic mechanism was proposed for organocatalytic reduction by several research groups (Scheme 1-36).[133,134,136] Firstly, ketimine is activated by protonation

with a chiral phosphoric acid to form a tight ion pair salt. Subsequently, hydride transfer from Hantzsch dihydropyridine to the iminium salt generates an enantiomerically enriched amine and pyridinium derivative.



Scheme 1-36. Proposed mechanism for organocatalytic reduction of imines with chiral acid.

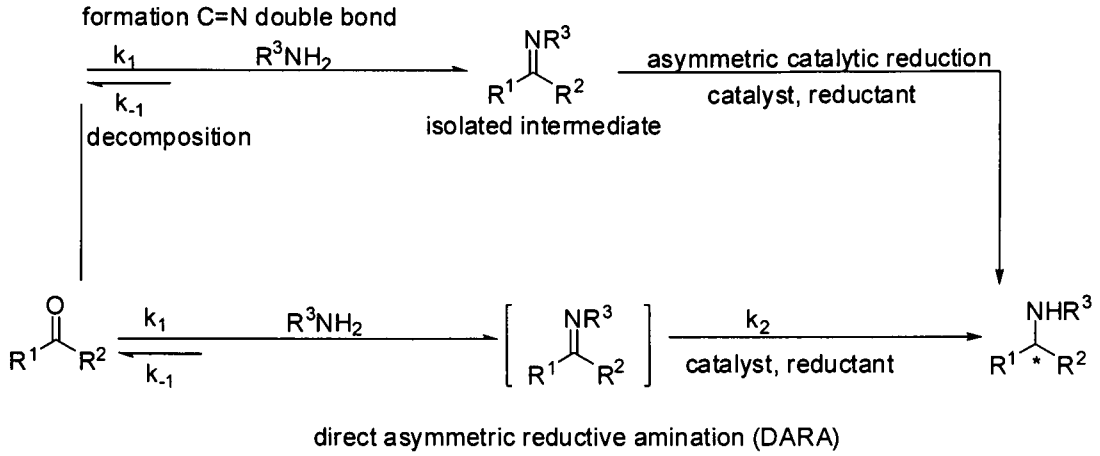
3. Direct Asymmetric Reductive Amination

3.1 Introduction

As described in previous sections, chiral amines could be accessed by asymmetric catalytic hydrogenation of imines. However, this powerful method requires the isolation of unsaturated imines for the sussequent reduction.[140,141] Owning to the equilibrium existing in the formation of imine, the imine may generally be obtained in a low isolated yield, by heating to 110 °C or by using $TiCl_4$ mediated reaction at room temperature.[74,79] In addition, the tedious purification need to be carried out quickly due to the limited stability of imines.

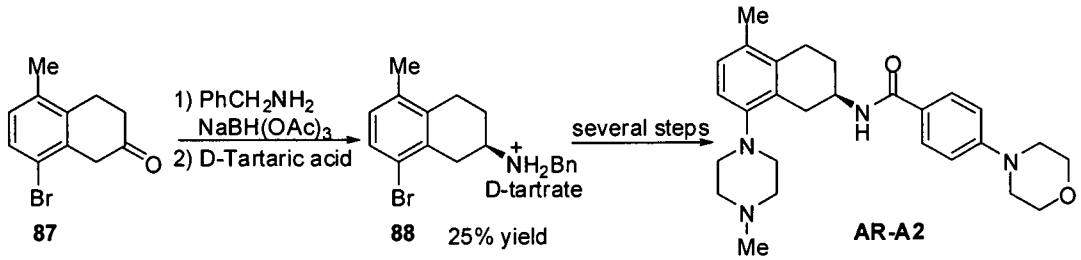
The one-pot two step reductive amination could be performed under milder conditions because the reduction step decreases the concentration of the intermediate imine, thus assisting the equilibrium to favour the formation of imine. Further, the one

pot reductive amination saves time and solvent. Therefore, the most convenient, economical, and eco-benign synthetic pathway to chiral amines is direct asymmetric reductive amination (DARA) of prochiral carbonyl substrate in a one-pot fashion (Scheme 1-37).



Scheme 1-37. Asymmetric reduction of imine and direct reductive amination.

Although DARA is a very convenient and efficient method for the synthesis of chiral amino fragnments, the method is far less developed so far.[136,140,141] For instance, AR-A2 is a new candidate drug displaying a pronounced antagonistic activity toward the 5-HT_{1B} receptor. The industrical process for generating the chiral amine **88** was nonasymmetric catalytic amination of ketone **87** with benzyl amine followed by chiral tartaric acid resolving the racemic enantiomers (Scheme 1-38). A more direct and economic synthetic route to intermediate **88** might start from compound **87** by DARA in one step.



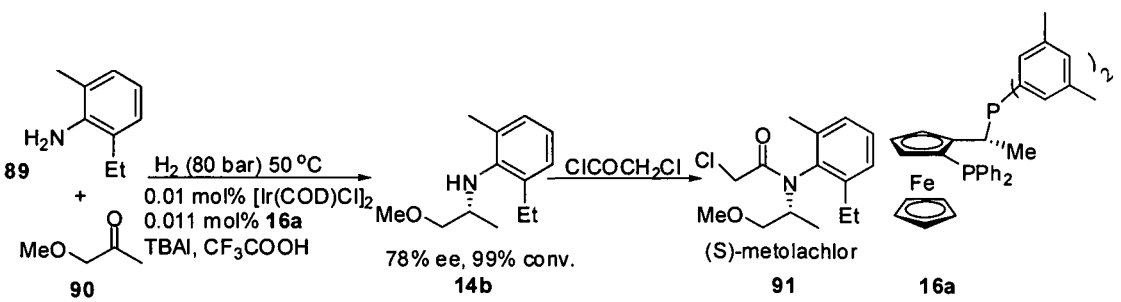
Scheme 1-38. Synthesis of pharmaceutical product AR-A2.

Owing to several reasons, the DARA has been less developed. On the one hand, DARA just has a history of ten years and results have not been emphasized enough in the past.[6,54] On the other hand, comparing to reduction of imines, the one-pot DARA is much more complicated and detailed mechanisms are not very clear to date. As is known, the DARA consists of two consecutive steps in one pot. The rate of reduction is determined by the slower step, and the enantioslectivity can be affected by the carbonyl compound or the partner amine. Blaser and coworkers found that the best productivity of catalyst in DARA remained 100 times lower than in the reduction of imine.[54] Borner and coworkers also found that the enantioselectivities in DARA were significantly lower than in reduction of the isolated imines in transition metal-catalyzed hydrogenation.[140] Chemoselectivity is another problem for the DARA process, because the existing carbonyl compound may also be reduced to the corresponding hydroxyl products instead of forming imines.[140]

Only a few DARA catalysts have been developed in the past ten years. It is noteworthy that one has been applied to an industrical process for the production of the herbicide Metolachlor.[54] The following sections provide a summary of the state of the art DARA of carbonyl compounds by hydrogenation or transfer hydrogenation.

3.2 Transition Metal-Catalyzed DARA

The first example of transition metal-catalyzed DARA was established by Blaser and co-workers in 1999 (Scheme 1-39).[54] A 78% ee was obtained for amine **14b** by DARA of methoxyacetone **90** with 2-methyl-5-ethyl-aniline (MEA) **89** by using their Ir-**16a** catalyst, which has been used for the hydrogenation of isolated imines.[54,56] Various solvents, iodide salts and acids were examined for the reaction. The catalyst displayed higher activity and enantioselectivity in the presence of a small amount of trifluoroacetic acid (CF_3COOH) and iodide ions in cyclohexane, leading to 99% conversion and 78% ee at a substrate to catalyst ratio of 10000 in 16 h. Although the result is quite remarkable to date, the productivity of the catalyst in DARA remained much lower than in the reduction of the corresponding isolated imine. The reason for this could either be a strong complexation of MEA, thus blocking the imine to access the iridium, or dimerization of Ir-**16a** to form an inactive species.

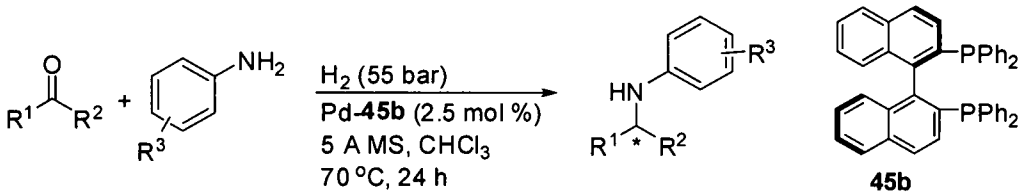


Scheme 1-39. Synthesis of (*S*)-Metolachlor by DARA of methoxyacetone.

Following the DARA of alphatic ketones,[54] DARA of other ketones was realized in very good yield with up to 99% ee by using an air stable Pd-phosphine catalyst.[142]

Selected results can be seen in Table 1-18. Several preformed chiral Pd-diphosphine complexes, in which the structure of [(*R*)-**45b**]$PdBr_2$ and (*S*,*S*)-**49**]$PdBr_2$ was characterized by X-ray, were examined for DARA of aliphatic and aromatic ketones. In the investigation by Rubio-Perez et al, a ligand with larger bite angle and better flexibility appear to be crucial for obtaining high conversion and enantioselectivity.[142] Using optimized conditions, a range of alphatic *N*-aryl amines were obtained in 51-84% isolated yield and up to 99% ee (entries 1-3). Lower yield was obtained when *p*-methyl aniline was replaced by more electron deficient *p*-trifluoro aniline (entries 1 and 2). However, the catalyst displayed lower enantioselectivity in the amination of acetophone or (*E*)-pent-3-en-2-one, even losing chemoselectivity in the reduction.

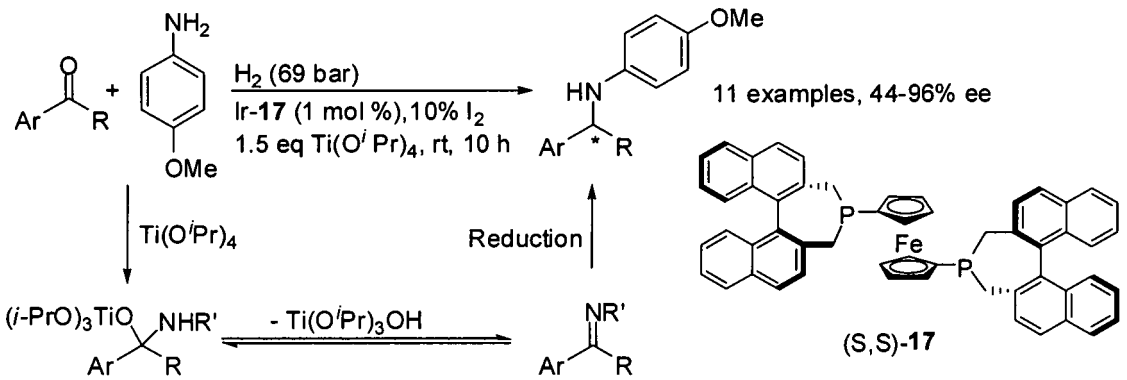
Table 1-18. Pd-**45b** catalyzed DARA of ketones



entry	R^1	R^2	R^3	yield., %	ee, %	config.
1	$CH_3(CH_2)_4$	CH_3	*p*-Me	84	73	(-)
2	$CH_3(CH_2)_4$	CH_3	*m*-CF_3	51	95	(-)
3	Et	Me	*p*-Me	77	99	(-)
4	$CH_3(CH)_2$	CH_3	H	78	10	(-)
5	C_6H_5	CH_3	H	64	43	*R*

Zhang and co-workers developed a DARA system for aromatic ketones by using 1% of Ir-f-Binaphane with 1.5 equivalent of $Ti(O^iPr)_4$ and 10% of I_2 (Scheme 1-40).[143] Based on their studies, $Ti(O^iPr)_4$ significantly promoted the formation of the imine,

enhancing the possibility for a high conversion in DARA of ketones. An aminoalcohol Ti (IV) complex was supposed to form, followed by formation of imines and then reduction in the presence of I_2. Iodine was assumed to assist Ir-**17** for hydrogenation of the resulting imines. A range of aromatic ketones were aminated with *p*-anisidine in 44-96% ee. The chiral primary amine was generated by using CAN to remove the protect group. However, the catalytic system did not work for reductive amination of alkyl ketones.

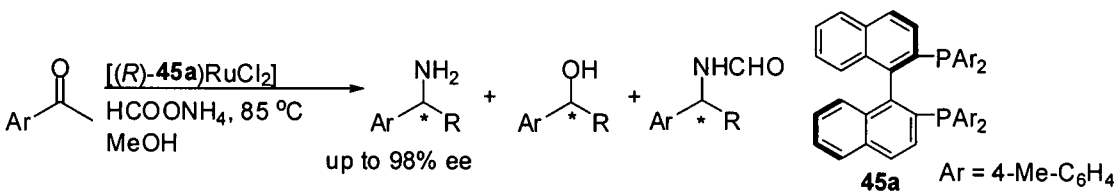


Scheme 1-40. DARA of aromatic ketones in the presence of $Ti(O^iPr)_4$.

In the above study, the secondary amines could be converted to primary amines by removing the protecting group. However, Kadyrov and coworkers realized the DARA of ketones with ammonium by using the catalyst [Ru((*R*)-**45a**)Cl_2], generating primary amines under transfer hydrogenation (Table 1-19).[144] A range of combinations involving Ru, Rh, and Ir complexes, diphosphines and diamine ligands were examined for the DARA of ketones with ammonium. When the reaction was carried out with 5 to 10 equivalents of $HCOONH_4$ in NH_3/methanol (15-25%) at 60-85 °C, 95% ee was

observed using the catalyst [Ru((*R*)-**45a**)Cl_2] (entry 1). Under optimized conditions, various enantiomerically enriched primary amines and *N*-formyl derivatives were afforded in up to 24-98% ee. However, DARA of alphatic ketone only led to 24% ee (entry 4). Although the *N*-formyl derivatives can be converted to primary amines after hydrolysis, the limited selectivity and additional step reduce its importance.

Table 1-19. [Ru((*R*)-**45a**)Cl_2] catalyzed DARA of ketones

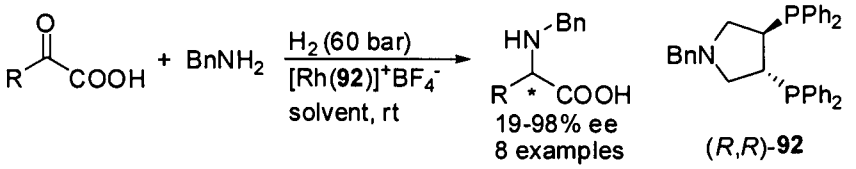


entry	substrate	t (h)	ketone (%)	amine (%)	formyl amine (%)	alcohol (%)	yield (%)	ee (%)
1	acetophone	20	5	75	19	1	92	95 (*R*)
2	4'-methylacetophone	21	0	8	91	0	93	93 (*R*)
3[a]	4'-nitroacetophone	48	0	45	55	0	92	95(*R*)
4	2-octanone	17	0	36	64	0	44	24 (*S*)

[a] 98% ee was obtained, when the reaction was carried out at 60 °C.

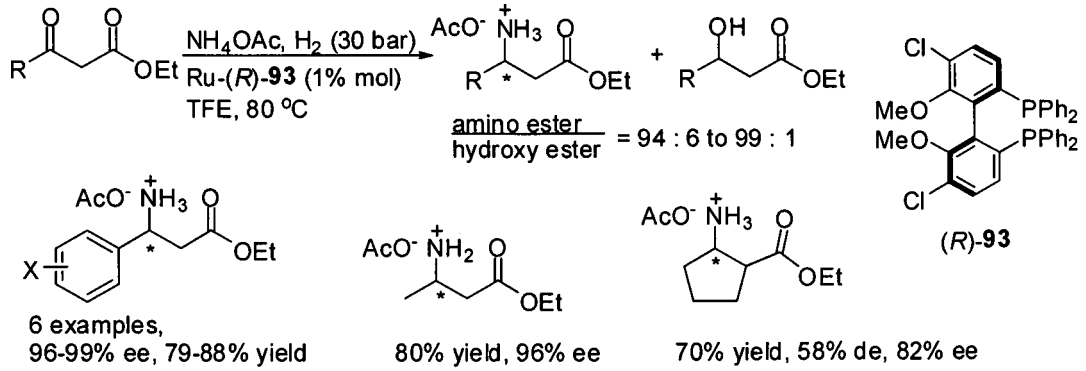
Clearly, DARA of keto acids is a valuable process for generating amino acids. To obtain an excellent catalyst for this reaction, Borner and co-workers tested a large number of precatalysts by high-throughput screening.[145] The catalyst was prepared in situ by the reaction of 96 chiral *P*-ligands with [$Rh(COD)_2$]BF_4 and [Rh(COD)Cl]$_2$, respectively (Scheme 1-41). The ionic [Rh(COD)(*R*,*R*)-**92**]BF_4 was found to be the

best catalyst judging from activity and enantioselectivity in the DARA of α-ketone acid with benzylamine. Using the Rh-**92** catalyst, seven *N*-benzyl alphatic amino acids were obtained in 73-98% ee, and *N*-benzylphenylglycine was also obtained, but only in 19% ee.



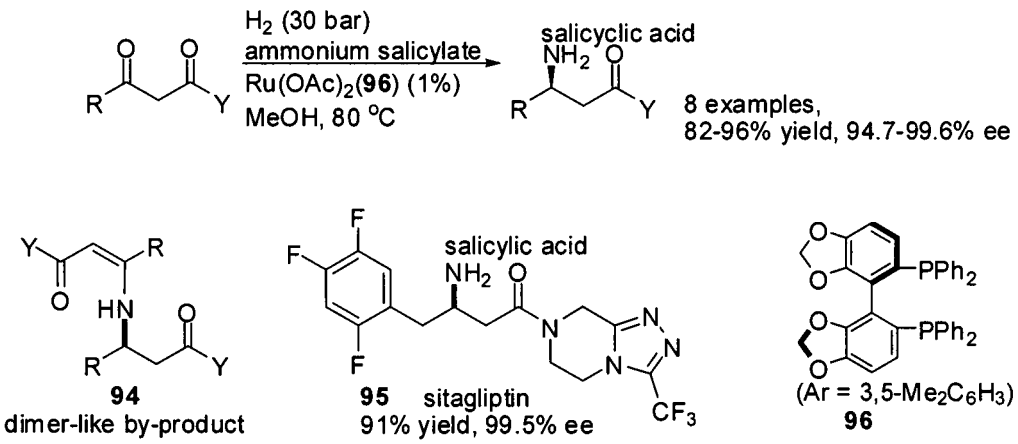
Scheme 1-41. DARA of α-keto acids with benzylamine catalyzed by Rh(I) complex.

In a related study, Bunlaksananusorn and Rampf demonstrated that DARA of a range of β-keto esters with ammonium acetate, generating β-amino esters in good yield and up to 99% ee by using Ru-**93** at 30 bar hydrogen pressure (Scheme 1-42).[146] It is noteworthy that cheap ammonium acetate was employed as the nitrogen source and the unprotected β-amino esters were formed during the reaction. Six aryl substituted β-amino ester salts were obtained in 96-99% ee and 79-88% yield along with some β-hydroxy ester. Alphatic ethyl-3-aminobutanoate was also obtained in 96% ee and 80% yield. Furthermore, cyclic β-amino ester salts containing two chiral centres were obtained. Imino ester was a possible intermediate for the reduction step. Good enantioselectivities were observed in all cases, probably because the intermediate, nonprotected imino ester does not exist as a mixture of *E*- and *Z*-isomers during the reaction.



Scheme 1-42. DARA of β-keto esters with amonium catalyzed by Ru(I) catalyst.

Quiet recently, DARA of β-keto amide with ammonium salicylate to produce unprotected β-amino amide was established by using the catalyst $Ru(OAc)_2$(**96**) in MeOH at 80 °C (Scheme 1-43).[147]

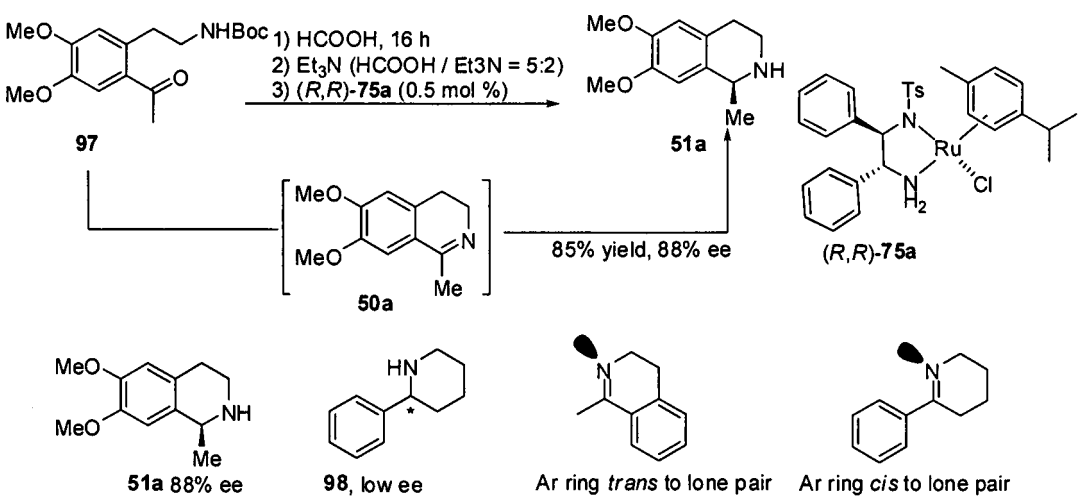


Scheme 1-43. DARA of β-keto amides with amonium catalyzed by Ru(II) catalyst.

In the presence of 1% $Ru(OAc)_2$(**96**) and 5 equiv of ammonium salicylate, sitagliptin **95**, a potent DPP-IV inhibitor, was obtained in 91% yield and 99.5% ee in MeOH. Ammonium salts containing different anions, solvents, and various catalysts were screened; and the additional 4 equiv of ammonium salicylate was found to be crucial to achieve high yield because it suppressed the dimer **94** formation or broke up

the dimer during the reaction. Under the optimized conditions, a range of β-amino amides were obtained in 82-96% yield and 94.7-99.6% ee.

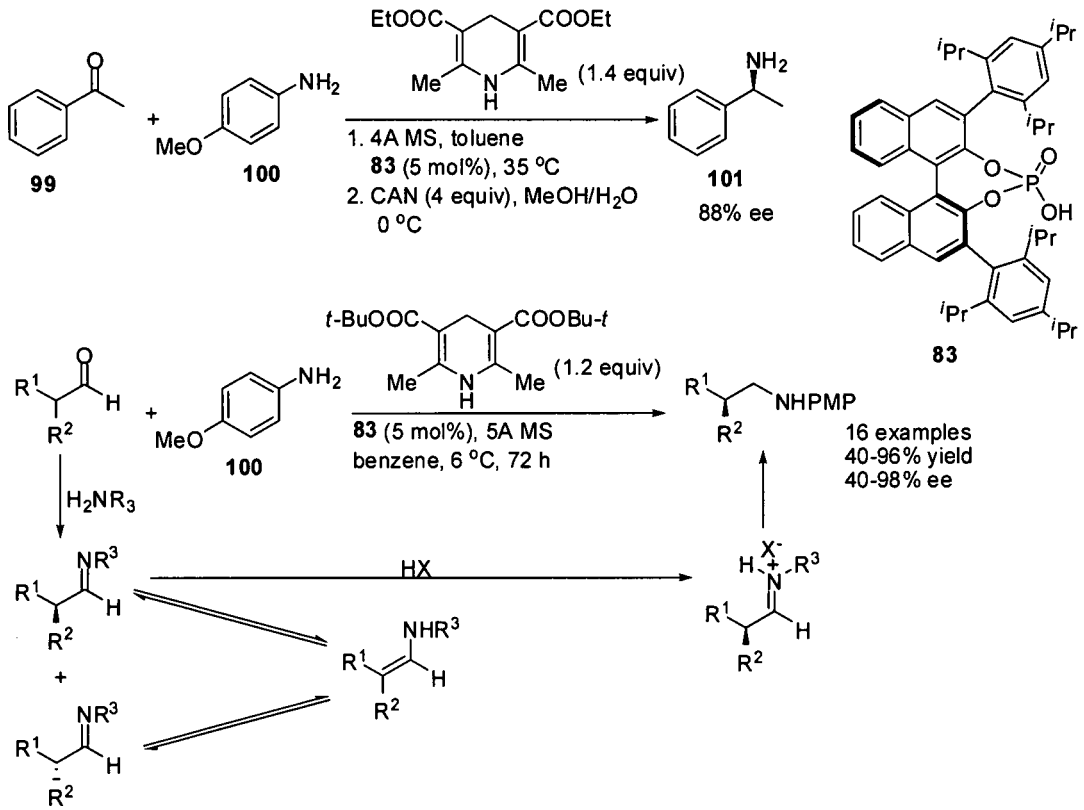
DARA of ketones to generate cyclic amines is unusual. Wills and co-workers developed an efficient catalytic system to produce enantiomerically enriched tetraisoquinoline **51a** by using (*R*,*R*)-**75a** under transfer hydrogenation conditions (Scheme 1-44).[148,149] The one-pot reductive amination proceeds in two consecutive steps; the first step is formation of the cyclic imine **50a** via deprotection of *t*-Boc-protected amino ketone **97**. This is followed by reduction of **50a** with (*R*,*R*)-**75a** by using the hydrogen source HCOOH-Et_3N. **51a** was obtained in 88% ee and 85% yield. Amine **98** was also obtained under similar conditions, but with almost no enantioselectivity. The reason for this is not entirely clear. The direction of the aromatic ring on the imine was considered important to achieve high enantioselectivity, because the aromatic ring on the side of imine lone pair could conflict with the catalyst, leading to loss of enantioselectivity in the reduction.



Scheme 1-44. DARA of ketones to generate tetraisoquinoline **51a**.

3.3 Organocatalytic Asymmetric Reductive Amination

The first example of one-pot organocatalytic reductive amination of ketones was reported by List and co-workers in 2005 (Scheme 1-45).[134]

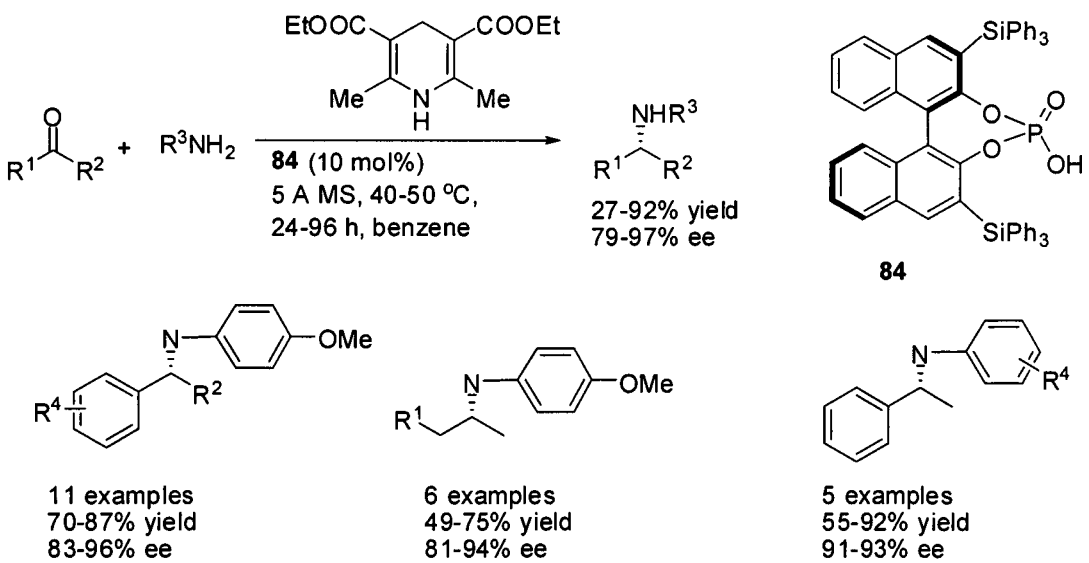


Scheme 1-45. DARA of ketone and α-branched aldehydes reported by List.

The primary amine **101** was obtained in 88% ee by using CAN to remove the protected group 4-methoxy-*N*-(1-phenylethylidene)aniline. The protect amine was produced by reduction of the in situ prepared imine in the presence of the phosphoric acid **83** prior to addition of Hantzsch ester. Subsequently, DARA of α-branched aldehydes to generate chiral β-branched amines was established by the same group (Scheme 1-45).[150] A dynamic kinetic resolution was assumed, in which one of the imine enantiomers was reduced faster than that of the other, but they would undergo

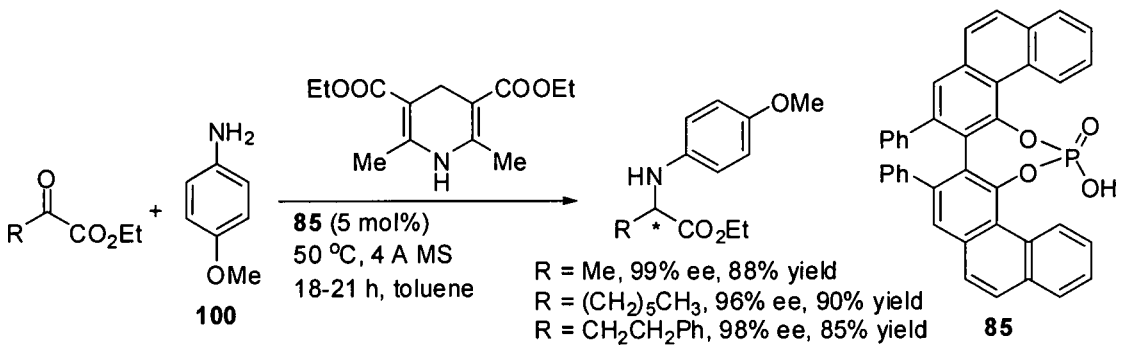
fast racemization via imine/enamine tautomerization in the presence of acid. Based on this concept, DARA of various α-branched aldehydes with *p*-anisidine was performed by using the catalyst **83**, leading to chiral β-branched amines with 40-96% yield and 40-98% ee.

Simultaneously, MacMillan and co-workers developed a highly efficient DARA of ketones with various primary amines, generating chiral secondary amines with good isolated yield and excellent enantioselectivity (Scheme 1-46).[136] Various Akiyama-Terada phosphoric acids were screened in the reaction. The phosphoric acid **84** was selected as the best catalyst for achieving good conversion and excellent enantioselectivity. Using optimized conditions, a range of aromatic and alphatic *N*-aryl amines were obtained in 83-96% ee and 81-94% ee, respectively; and various electronically diverse amines were also obtained, in 91-93% ee.



Scheme 1-46. MacMillan's catalytic system for DARA of ketone.

As described in Section 2.4.2, Antilla and co-workers developed an excellent catalytic system for the reduction of α-imino esters.[137] In the same paper, they also reported three examples of α-keto esters that were directly aminated with *p*-anisidine by using the catalyst **85** in the presence of Hantzsch ester. The α-amino esters were obtained in 88-90% yield and 96-99% ee (Scheme 1-47).



Scheme 1-47. Antilla's catalytic system for DARA of α-keto esters.

4 Conclusion

In Section 1, tetrahydroquinoline and tetrahydro-β-carboline have been mentioned as very important pharmaceticul products or building blocks in the synthesis of natural product. However, apart from Buchwald's titanocene catalyst that allows a tetrahydroisoquinoline to be obtained in 98% ee, all the reported hydrogenation catalysts afforded less than 90% ee for tetrahydroquinoline and tetrahydro-β-carboline. Furthermore, only a few examples of these compounds have been demonstrated with good to excellent enantioselectivity by using Noyori type Ru/Rh-TsDPEN catalyst under transfer hydrogenation. A more efficient and simpler hydrogenation of cyclic

imines to these compounds is desired. As summarised in Sections 2 and 3, various catalysts have been applied to enantioselective hydrogenation of C=N functions and DARA of carbonyl compounds to generate chiral amines, affording good to excellent enantioselectivities. However, most of the transition metal catalysts show low activity, low enantioselectivity or narrow substrate scope. In contrast, chiral phosphoric acids are potentially excellent catalysts. However, the enantiomerically enriched amines could generally be obtained only over long reaction times. A more versatile catalyst will be desired for those enantioselective hydrogenation and DARA systems.

In response to those challenges, three areas of research have been carried out in the past three years and are presented in this thesis. Firstly, catalytic hydrogenation of cyclic imines to generate tetrahydroquinoline and tetrahydro-β-carboline will be described in Chapter 2. Secondly, an excellent cooperative catalytic system comprised of a chiral phosphoric acid and a transition metal will be described in Chapter 3. Thirdly, in Chapter 4, we will also show a metal catalytic system for DARA by using chiral counteranion together with a chiral Brønsted acid.

5. References

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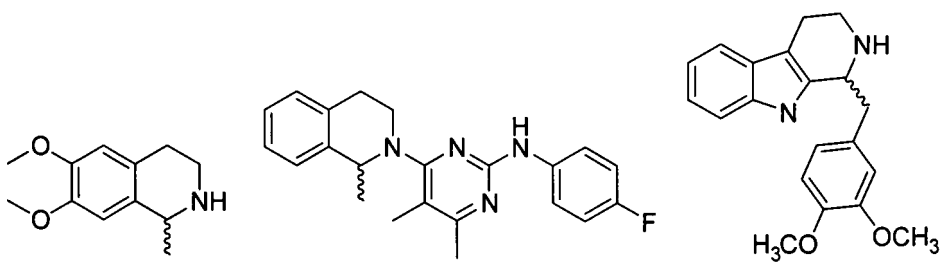
Chapter 2. Asymmetric Hydrogenation of Cyclic Imines with an Ionic Cp*Rh(III)-TsDPEN Catalyst

1 Introduction

Tetrahydroisoquinoline and tetrahydro-β-carboline rings are widely existing structure units in alkaloids, and their derivatives are known to display high bioactivities (Scheme 2-1).[1] For instance, salsolidine is a naturally occurring alkaloid,[1b] while YH 1885 is of interest for the treatment of gastro-oesophageal reflux disease and duodenal ulcers.[2] A further example is the tetrahydro-β-carboline LY23728, an antagonist for the serotonin 2B receptor.[3] Whilst methods for the asymmetric synthesis of these molecules have been developed,[1d,4] including chiral auxiliaries[4a,e] and organocatalysis,[4b,c] a straightforward, "greener" method is asymmetric hydrogenation of the corresponding imines, which can be readily derived from the Bischler-Napieralski cyclization.[5]



Salsolidine YH1885 LY23728

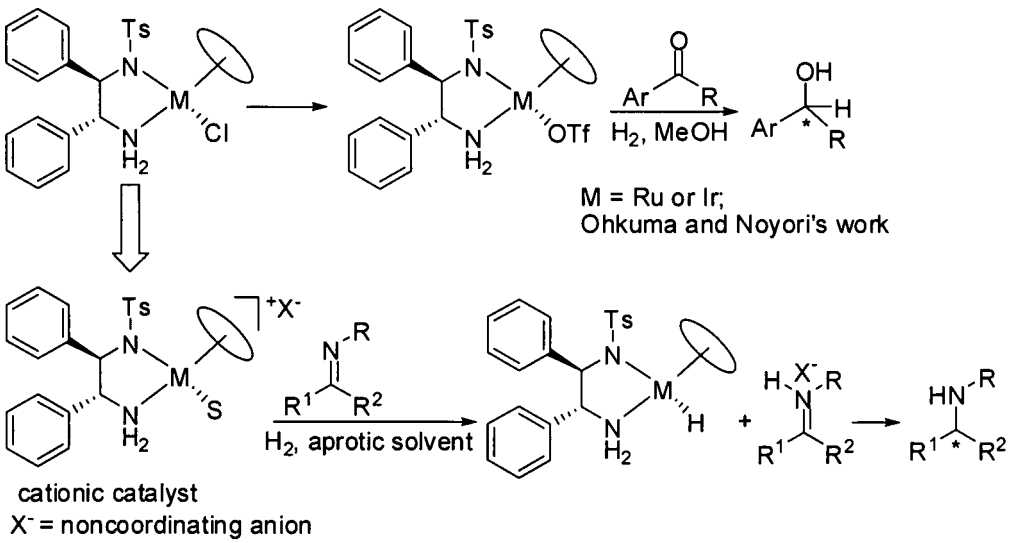
Scheme 2-1. Representive examples of tetrahydroisoquinoline and tetrahydro-β-carboline

Although many excellent catalysts are now available for the asymmetric hydrogenation of olefins and ketones,[6] developing catalysts for the closely related imines remains a considerable challenge.[7] And this is the case with both acyclic and

cyclic imines, although the latter are devoid of the problematic *syn/anti* isomerisation. In the particular case of isoquinoline-type imines, there are only a few papers thus far, reporting on the formation of tetrahydroisoquinolines and tetrahydro-β-carbolines under either hydrogenation[8] or transfer hydrogenation[9] conditions. Buchwald's titanium hydrogenation catalyst allows 1-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline to be obtained in 96% ee; but its application potential is rather low due to the low TOFs and difficulty in handling.[7,8a] Better rates (TOF: 5 h^{-1}) were achieved with iridium-diphosphine catalysts, although the ee's were lower (<90%) and a higher H_2 pressure was used (100 bar).[8e] Recently, a ruthenium-diphosphine catalyst was shown to give a 89% ee in the hydrogenation of 1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline.[8k] Still better results were obtained under transfer hydrogenation conditions with the Noyori-Ikariya Ru-TsDPEN (TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine) catalyst, with ee's of up to 96% being observed.[9a]

Clearly, much remains to be done in discovering viable catalysts that use the desirable H_2. Very recently work, Noyori, Ohkuma and coworkers discovered that Ru(OTf)(TsDPEN)(*p*-cymene) and a Cp*Ir(III) analogue are excellent catalysts for ketone hydrogenation in methanol.[10] The alcohol was supposed to be a base that assists catalytic heterolytic cleavage of hydrogen to form metal-hydride and the alcohol synchronously accepts a proton to form oxonium by hydrogen bonding. We thought the alcohol could be replaced by a catalytic amount of a strong base or basic substrate. Based on this concept, our group have shown that a related Cp*Ir-Cl complex with

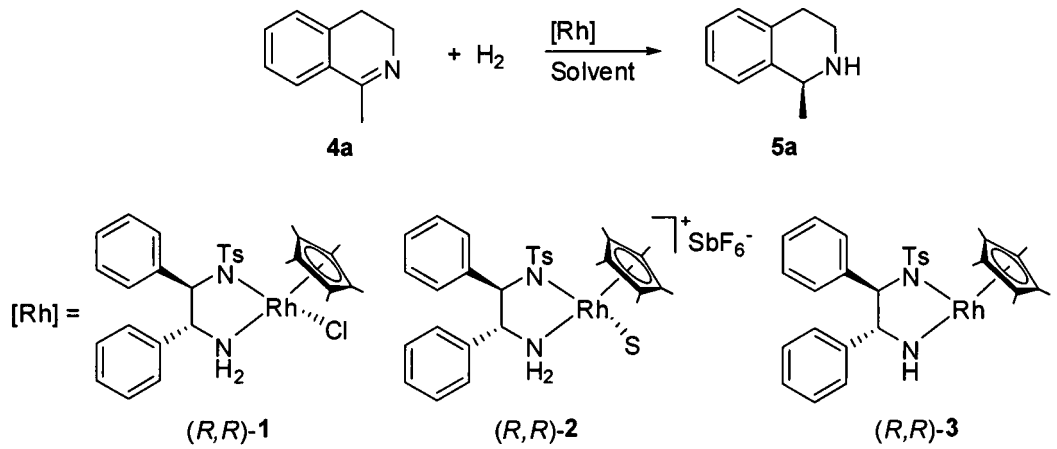
5-10 equiv KOH enables fast hydrogenation of aldehydes in water.[11] Because we are particularly interested in synthesis of chiral amines via catalytic enantioselective reduction of imines, we presumed an efficient cooperative catalytic system in which the imine acts as a base assisting the heterolytic splitting of hydrogen to form metal-hydride and iminium salt, with the imine directly accepting a proton from the splitting dihydrogen (Scheme 2-2). Based on this concept, we developed an ionic TsDPEN-ligated Rh(III) catalyst that enables highly efficient asymmetric hydrogenation of cyclic imines to afford tetrahydroisoquinolines and tetrahydro-β-carbolines under mild conditions. To the best of our knowledge, no diamine ligand was successfully demonstrated in asymmetric hydrogenation of imines before we started this project.[12]



Scheme 2-2. Proposed catalytic system for asymmetric hydrogenation of imines.

2 Results and Discussion

2.1 Additive Effect



Scheme 2-3. Rhodium catalyzed asymmetric hydrogenation of the cyclic imine **4a** (S = solvent).

The Rh-TsDPEN complex **1** is an excellent catalyst for asymmetric transfer hydrogenation of ketones using either isopropanol or formate salts as hydrogen source (Scheme 2-3).[13] We set out by examining **1** for a model hydrogenation using the cyclic imine **4a** as substrate. The hydrogenation was initiated by introducing 20 bar H_2 into an autoclave charged with **4a** and **1** (0.5 mol%) in dichloromethane (DCM) at room temperature. No reduction was observed in either 0.5 h or a prolonged time of 4 h under such conditions. A 2% conversion was observed when the reduction was carried out for 24 h. Making the reaction condition more basic by adding Et_3N, KOH or *t*-BuOK did not bring about any significant changes in 0.5 h, or a prolonged time of 24 h. In contrast, acidic conditions can bring about a 4% conversion in 0.5 h. A slightly improved conversion of 14% and 65% ee were observed in the presence of 5% benzoic

acid after 24 h. The screening results are shown in Table 2-1.

Table 2- 1: Additive effect in asymmetric hydrogenation of **4a**.[a]

entry	solvent	time (h)	additive	conv. (%)[b]	ee (%)[c]
1	DCM	0.5	No	0	n.d.
2	DCM	4	No	0	n.d.
3	DCM	24	No	2	n.d.
4	DCM	0.5	Et_3N	0	n.d.
5	DCM	0.5	KOH	0	n.d.
6	DCM	0.5	t-BuOK	0	n.d.
7	DCM	0.5	Benzoic acid	4	n.d.
8	DCM	24	Et_3N	3	n.d.
9	DCM	24	KOH	2	n.d.
10	DCM	24	t-BuOK	4	n.d.
11	DCM	24	Benzoic acid	14	65

[a] Reaction conditions: 0.5 mmol cyclic imine, 0.5 mol% **1** (2.5 μmol), 5% additive when added, 2 mL DCM, 20 bar H_2 at room temperature. [b] Determined by ^1H NMR analysis of the crude products. [c] Determined by GC analysis with a chiral Beta DEX-120 column; n.d. = not determined.

From the recent work of Noyori[10b] and Rauchfuss,[14] one would expect that the corresponding cationic Rh(III) species might be more reactive towards H_2 and particularly towards its heterolytic splitting to form the Rh-H hydride and proton. With this in mind, we then tested the effect of silver salts on the reduction, aiming to remove the chloride from the coordination sphere. As can be seen from Table 2-2, upon introduction of a silver salt, some reduction did take place in 0.5 h. However, the

combination of **1** with siliver bearing a range of anions, such as noncoordinating SbF_6^-, BF_4^-, PF_6^-, weakly coordinating OTf^- and coordinating OAc^-, PO_4^- and ClO_4^-, showed similar activities for hydrogenation of **4a** under 20 bar hydrogen pressure in dried CH_2Cl_2 (entries 1-7). Much to our delight, a remarkably accelerated reduction was observed in the case of $AgSbF_6$, in the wet CH_2Cl_2; a 20% conversion was recorded, with **5a** being produced in an excellent ee of 99% (entry 8).

Table 2-2: Effect of anions in asymmetric hydrogenation of **4a**.[a]

entry	solvent	additive	conv. (%)	ee (%)
1	DCM	$AgSbF_6$	6	n.d.
2	DCM	$AgBF_4$	3	n.d.
3	DCM	$AgPF_6$	3	n.d.
4	DCM	AgOAc	2	n.d.
5	DCM	AgOTf	3	n.d.
6	DCM	Ag_3PO_4	1	n.d.
7	DCM	$AgClO_4$	1	n.d.
8	DCM[b]	$AgSbF_6$	20	99

[a] Reaction conditions: 0.5 mmol cyclic imine, 0.5 mol% **1** (2.5 μmol), 2 mol% siliver salt, 2 mL DCM, 20 bar H_2 at room temperature for 0.5 h. [b] wet DCM.

Following this observation, we started to examine the effect of water on the asymmetric hydrogenation of **4a** in the presence of **1** (0.5 mol%) with $AgSbF_6$ (2.0 mol%) in distilled DCM. The results can be seen in Table 2-3. Introduction of increasing quantities of water into the reaction indeed increased the conversion; the highest conversion of 36% was recorded when the molar ratio of water to substrate

was 3.3 in 2 mL CH_2Cl_2, with **5a** being produced in an excellent ee of 99%. Under such conditions, **1** is presumably converted into **2**, which bears a bulky counter anion SbF_6^-.[15] Subsequently, the conversion decreased as more water was added to the reaction (Table 2-3). Too much water somewhat decreased the ee value of product **5a** from 99% to 98%. As small amount of water was supposed to increase the solubility of $AgSbF_6$, thus increasing the concentration of active catalyst during the reaction. Because water is a coordinating solvent, too much water in solution might lead to coordination of the ionic catalyst, thus decreasing the concentration of active catalyst.

Table 2-3. Effect of small amount of water for asymmetric hydrogenation of **4a**.[a]

entry	solvent	(H_2O/imine)[b]	conv. (%)	ee (%)
1	DCM	0	6	n.d.
2	DCM	1.1	18	97
3	DCM	2.2	30	98
4	DCM	2.8	34	99
5	DCM	3.3	36	99
6	DCM	3.8	33	99
7	DCM	5.5	28	98
8	DCM	11.1	18	98

[a] Reaction conditions: 0.5 mmol cyclic imine, 0.5 mol% **1** (2.5 μmol), 2 mol% $AgSbF_6$, 2 mL dried DCM, 20 bar H_2 at room temperature for 0.5 h. [b] molar ratio of water to substrate

To understand the role of water and anions in the catalytic system, further investigations have been done by examining 0.5 mol% of **1** or the analogue with no additive, a small amount of Et_3N as additive, or a range of siliver salts in 2 mL DCM

containing 30 μl water. The screening results are shown in Table 2-4. Consistent with the ionic **2** being the key for hydrogen activation, catalyst **1** also showed no activity for the hydrogenation of **4a** under such conditions, as well as in the basic conditions by introducing 5% Et_3N (entries 1 and 2). The catalyst derived from $AgBF_4$, $AgPF_6$, or AgOTf, which contain a noncoordinating anion BF_4^-, PF_6^- or weakly coordinating anion OTf^-, led to a conversion of only 4%, 3%, 4% respectively in 0.5 h (entries 4 to 6); and the similar catalyst which contained a coordinating anion OAc^-, PO_4^{3-}, or ClO_4^- led to a conversion of only 2% in 0.5 h (entries 7, 9 and 10). A 10% conversion and 60% ee were observed when the reaction was carried out for 10 h by using the catalyst bearing OAc^-. Furthermore, when the 16e species **3** (Scheme 2-3) was used to replace **2**, no hydrogenation took place (entry 11) in the presence of 30 μl water. However, hydrogenation occurred when $HSbF_6$ was introduced, indicating that **3** is protonated, *in situ* affording the active catalyst **2** (entry 4).[16] The preformed catalyst **2** showed a similar activity and enantioselectivity to the in situ catalyst in DCM containing 30 μl of H_2O (entries 3 and 12), but **2** showed silightly higher activity in dried CH_2Cl_2 (entry 13). However, addition of 2 equiv. Bu_4NBr (relative to rhodium) completely stopped the hydrogenation with **2** (entry 14). The analogue of **2**, i.e. in situ generated ionic ruthenium and iridium catalyst, only afforded a conversion of 2% and 14% (92% ee) for hydrogenation of **4a** in 0.5 h, and 63% conversion (83% ee) by the ruthenium catalyst in 10 h (entries15-17). Still further, somewhat lower conversions were observed when the solvent was neat water, isopropanol (IPA), methanol (MeOH) or toluene (entries18-21).

Table 2-4: Effect of anion on asymmetric hydrogenation of **4a** in the presence of water.[a]

entry	solvent	time (h)	additive	conv. (%)	ee (%)
1	DCM	0.5	No	0	n.d.
2	DCM	0.5	Et_3N [b]	0	n.d.
3	DCM	0.5	$AgSbF_6$	36	99
4	DCM	0.5	$AgBF_4$	4	n.d.
5	DCM	0.5	$AgPF_6$	3	n.d.
6	DCM	0.5	AgOTf	4	n.d.
7	DCM	0.5	AgOAc	2	n.d.
8	DCM	10	AgOAc	10	60
9	DCM	0.5	Ag_3PO_4	2	n.d.
10	DCM	0.5	$AgClO_4$	2	n.d.
11[c]	DCM	0.5	No	0	n.d.
12[d]	DCM	0.5	No	33	99
13[e]	DCM	0.5	No	37	99
14[d]	DCM	0.5	Bu_4NBr	0	n.d.
15[f]	DCM	0.5	$AgSbF_6$	2	n.d.
16[f]	DCM	10	$AgSbF_6$	63	83
17[g]	DCM	0.5	$AgSbF_6$	14	92
18	H_2O	0.5	$AgSbF_6$	1	n.d.
19	IPA	0.5	$AgSbF_6$	18	98
20	MeOH	0.5	$AgSbF_6$	20	99
21	Toluene	0.5	$AgSbF_6$	30	99

[a] Reaction conditions: 0.5 mmol of cyclic imine, 0.5 mol% of **1** (2.5 μmol), 2 mol% of siliver salt when added, 2 mL of DCM, 30 μl of H_2O, 20 bar of H_2 at room temperature. [b] 2.5 mol% of Et_3N [c] 0.5 mol% of **3** as a catalyst [d] 0.5 mol% of **2** as a catalyst. [e] 0.5 mol% of **2** as catalyst in the absence of water [f] The analogous [RuCl(TsDPEN-H)(*p*-cymene)] as catalyst (1 mol% of catalyst, 4 mol% of silver salt). [g] 0.5 mol% of [Cp*IrCl(TsDPEN-H)] as catalyst.

This dramatic anion effect is further demonstrated by the kinetic profiles shown in Figure 2-1. Whilst **1** showed no reduction, the conversions effected by the corresponding OTf^- and PF_6^- salt were less than 20% in 4 h reaction time. By way of contrast, the in situ-generated **2** afforded a conversion of 93% (99% ee), and its initial rate was more than 5 times that of the OTf^- catalyst. This is surprising, as the related, weakly-coordinating OTf^- salt of Ru(II) and Ir(III) are active for ketone hydrogenation.[10] We note, however, that a similar effect of anions has previously been revealed by Pfaltz and coworkers in olefin hydrogenation with iridium catalysts containing P^N ligands.[17]

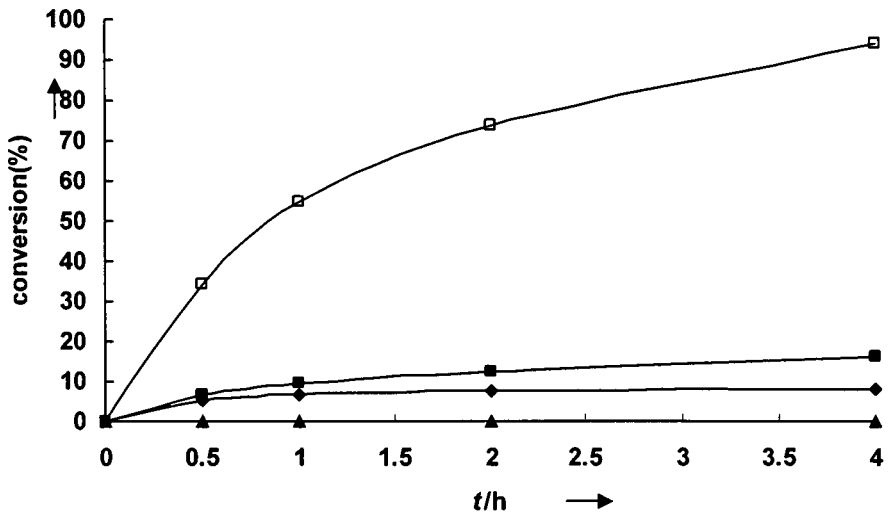


Figure 2-1. Effect of anions (▲ Cl^-, ♦ PF_6^-, ■ OTf^-, □ SbF_6^-) on the rate of hydrogenation of **4a** in DCM at room temperature. The catalysts were either **1** or *in situ* derived from **1** in the presence of a silver salt; see Table 2-4 (entries 6-13) for conditions.

2.2 Hydrogen Pressure Effect

The effect of hydrogen pressure has also have been investigated for the reduction. The hydrogenation rate, but not the enantioselectivity, varied with hydrogen pressure, as shown in Figure 2. As can be seen, the reaction rate increases almost linearly when the hydrogen pressure increased from 5 bar to 20 bar, and then the reaction rate gradually slows down when the hydrogen pressure exceeds 20 bar. It suggests that the hydrogenation rate is affected by the rate of formation of hydride and hydride transfer. Owing to the low concentration of hydrogen in solution at low pressure, the pressure-dependent step of hydride formation is rate-determining step in the whole reduction. As the hydrogen pressure increases, both the rate of hydride formation and the rate of hydride transfer affect the overall reaction rate.

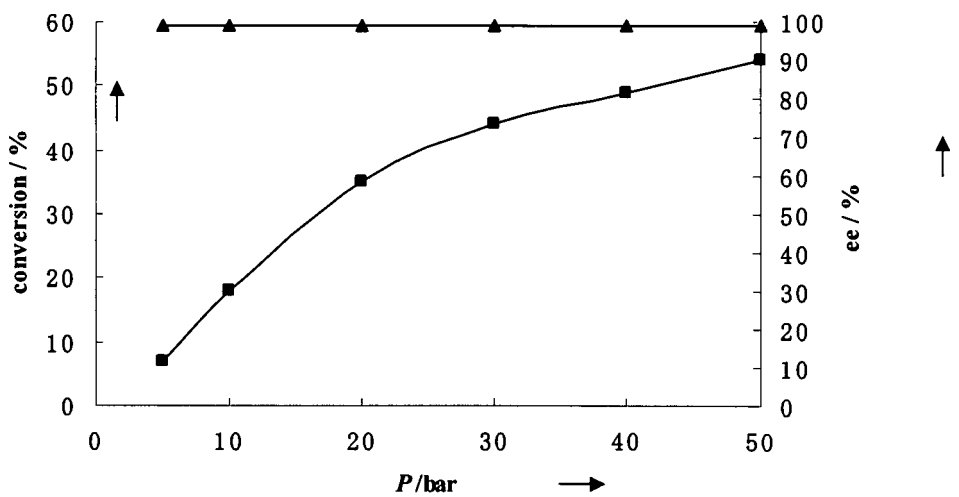
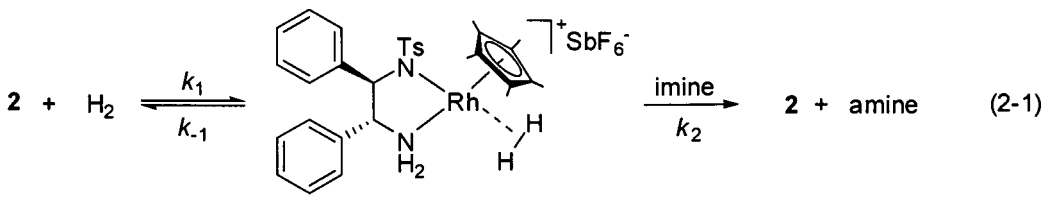


Figure 2-2. Effect of hydrogen pressure on the conversion (■) and enantioselectivity (▲) of hydrogenation of **4a** catalyzed by **2** (generated *in situ* from **1** and $AgSbF_6$) in DCM at room temperature for 0.5 h.

This observation supports a Michaelis-Menten type sequence as shown in Eq. 2-1. Evidently, the presence of coordinating anions such as Br^- will decrease the concentration of **2** and hence the hydrogenation rate.



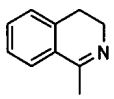
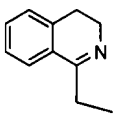
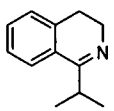
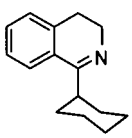
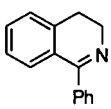
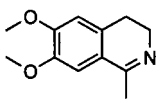
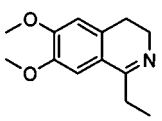
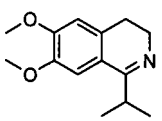
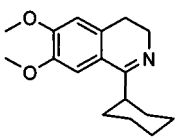
(2-1)

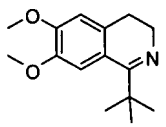
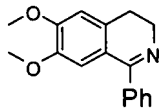
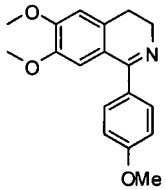
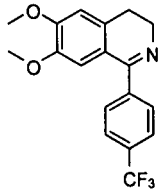
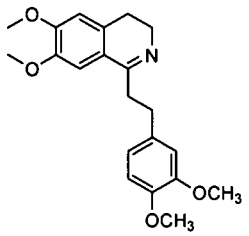
2.3 Asymmetric Hydrogenation of Cyclic Imines 4

Using the optimized conditions, *viz.* with **2** being generated *in situ* from **1** (1 mol%) and $AgSbF_6$ in the presence of 30 μl water at 20 bar hydrogen pressure, a range of cyclic imines **4** were hydrogenated to tetrahydroisoquinolones **5**. The results on 3,4-dihydroisoquinolines and 3,4-dihydro-6,7-dimethoxyisoquinolines are given in Table 2-5. As can be seen, **4a** was completely reduced, affording **5a** in 99% ee and 94% isolated yield in 1 h at room temperature (entry 1). However, replacing the methyl with the bulkier Et, ^{i}Pr, Cy and Ph substituents necessitated longer reaction times, and the enantioselectivity decreased significantly in the case of **4c**, **4d** and **4e** (entries 3-5). Surprisingly but delightfully, excellent yields and ee's were observed for 3,4-dihydro-6,7-dimethoxyisoquinolines. Thus, the compounds **4f-4i** and **4n** were all fully reduced in 4-5 h, with ee's up to 99% being obtained. These results suggest that the poor behaviour of **4c** and **4d** cannot simply be ascribed to steric effects. Since the enantioselectivity of the hydrogenation may be determined by weak C-H π interactions

between the Cp* methyl group and the imine aromatic ring,[18] the more electron-rich **4h** and **4i** might be expected to give rise to stronger interactions and so higher ee's. However, the catalytic system showed less efficiency with the much bulkier *t*-Bu, Ph, 4-MeO-Ph and 4-CF_3-Ph substituted substrates in either activities or enantioselectivities (entries 10-13) under such conditions.

Table 2-5: Asymmetric hydrogenation of cyclic imines **4** to give amines **5**.[a]

Entry	4	substrate	time (h)	solvent	yield (%) [b]	ee (%) [c]
1	**4a**		1	DCM	94	99[d]
2	**4b**		8	DCM	95	97
3	**4c**		4	DCM	90	40
4	**4d**		4	DCM	90	65
5	**4e**		24	DCM	30	8
6	**4f**		4	DCM	95	96
7	**4g**		4	DCM	90	93
8	**4h**		4	DCM	95	93
9	**4i**		4	DCM	94	95

Entry	4	substrate	time (h)	solvent	yield (%) [b]	ee (%) [c]
10	**4j**		24	DCM	8 [e]	n.d.
11	**4k**		24	DCM	25	5
12	**4l**		24	DCM	30	8
13	**4m**		24	DCM	10 [e]	n.d.
14	**4n**		5	DCM	95	99

[a] Reaction conditions: 0.5 mmol **4**, 1 mol% **1**, 4 mol% $AgSbF_6$, 2 mL DCM, 30 μL water, 20 bar H_2 at room temperature. [b] Isolated yields, after flash chromatography. [c] *S* product, determined by HPLC analysis with a chiralpak OD-H column. [d] Determined by GC; see Table 1. [e] conversion, determined by ^{1}H NMR analysis of the crude product.

In contrast to **5e** and **5j-5m** where both low conversion and low ee's were obtained, **5c** and **5d** were obtained in good conversion but medium ee's under those conditions. For **5c** and **5d**, we focused on increasing their ee's by optimization of reaction conditions. Various silver salts and solvents with or without water were examined for hydrogenation of **4c** and **4d**. The screening results are seen in Table 2-6. Consistent with the former observation on hydrogenation of **4a**, the ionic catalyst **2**, in situ from **1**

and $AgSbF_6$, showed higher activities and enantioselectivities for hydrogenation of **4c** than the catalyst formed from **1** and $AgBF_4$ (entries 1-4).

Table 2-6: Optimization of conditions for the hydrogenation of **4c** and **4d**.[a]

entry	4	additive	time (h)	solvent	conv. (%) [b]	ee (%) [c]
1	**4c**	$AgBF_4$	4	DCM	30	30
2	**4c**	$AgSbF_6$	4	DCM	67	38
3	**4c**	$AgBF_4 + H_2O$	4	DCM	25	32
4	**4c**	$AgSbF_6 + H_2O$	4	DCM	95	40
5	**4c**	$AgSbF_6$	4	CH_3CN	2	n.d.
6	**4c**	$AgSbF_6 + H_2O$	4	CH_3CN	2	n.d.
7	**4c**	$AgSbF_6$	4	MeOH	38	78
8	**4c**	$AgSbF_6 + H_2O$	4	MeOH	45	80
9	**4c**	$AgSbF_6 + H_2O$	4	TFE	40	63
10	**4c**	$AgSbF_6 + H_2O$	4	IPA	43	83
11	**4c**	$AgSbF_6 + H_2O$	24	IPA	85	83
12[d]	**4c**	$AgSbF_6 + H_2O$	24	IPA	97	83
13	**4d**	$AgSbF_6 + H_2O$	4	DCM	95	65
14	**4d**	$AgSbF_6 + H_2O$	4	MeOH	50	88
15	**4d**	$AgSbF_6 + H_2O$	4	IPA	45	91
16	**4d**	$AgSbF_6 + H_2O$	24	IPA	88	91
17[d]	**4d**	$AgSbF_6 + H_2O$	24	IPA	99	91

[a] Reaction conditions: 0.5 mmol **4**, 1 mol% **1**, 4 mol% siliver salt when added, 2 mL solvent, 30 μL water when added, 20 bar H_2 at room temperature. [b] Determined by ^1H NMR analysis of the crude products. [c] *S* product, determined by HPLC analysis with a chiralpak OD-H column. [d] 50 bar hydrogen pressure.

Furthermore, the ionic **2** was found to almost completely lose activity in strongly coordinating solvents such as CH_3CN with or without water (entries 5 and 6). When the solvent was changed to isopropanol (IPA), the ee's were improved to 83% and 91% for **5c** and **5d** respectively (entries 10 and 15). However, compared to the reaction in DCM, the ionic **2** showed lower activities in methanol, IPA and TFE; and the hydrogenation of **4c** and **4d** could not completely be finished after 24 h. Finally, **5c** and **5d** were obtained in 83% ee (97% conversion) and 91% ee (99% conversion) respectively, by increasing the hydrogen pressure to 50 bar in 24 h.

The observations showed that hydrogen pressure affects the reaction rate and solvent affects the ee of product. In order to improve the conversion and ee's of **5e** and **5j-5m**, **4e** was selected as a model for the optimization of conditions by using ionic **2** under various hydrogen pressures in DCM or MeOH with or without water (Table 2-7). A 24% and 18% conversion of **4e** was obtained, respectively, in DCM with or without 30 μL water in 5 h, and the conversion increased to *ca* 30% in 20 h (entries 1-4); the conversion was improved to 45% by increasing the hydrogen pressure to 55 bar in 20 h (entries 5-8). Furthermore, in contrast with the observation on hydrogenation of **4c** and **4d**, **5e** was obtained in 8% ee in both DCM and methanol. Catalyst **2** showed less efficiency for hydrogenation of **4e**, probably because the chiral diamine ligand was replaced by the substrate imine or product amine during the reaction, particularly as phenyl substituted imine can easily form cyclometallation complexs.[19]

Table 2-7: Optimization of conditions for the hydrogenation of **4e**.[a]

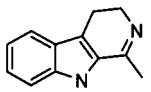
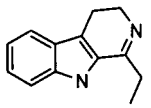
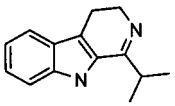
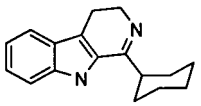
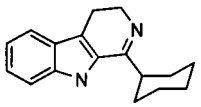
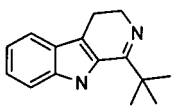
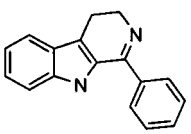
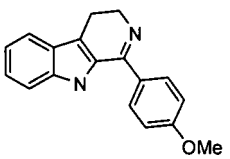
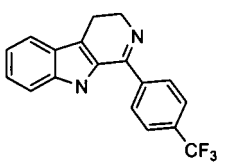
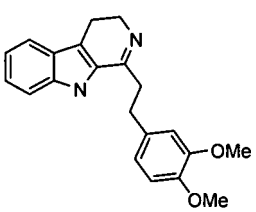
entry	additive	time (h)	pressure (bar)	solvent	conversion (%) [b]	ee (%) [c]
1	$AgSbF_6$	5	20	DCM	18	8
2	$AgSbF_6 + H_2O$	5	20	DCM	24	8
3	$AgSbF_6$	20	20	DCM	28	8
4	$AgSbF_6 + H_2O$	20	20	DCM	30	8
5	$AgSbF_6$	20	40	DCM	43	8
6	$AgSbF_6 + H_2O$	20	40	DCM	45	8
7	$AgSbF_6$	20	55	DCM	44	8
8	$AgSbF_6 + H_2O$	20	55	DCM	45	8
9	$AgSbF_6$	20	20	MeOH	22	8
10	$AgSbF_6 + H_2O$	20	20	MeOH	30	8

[a] Reaction conditions: 0.5 mmol **4e**, 1 mol% **1**, 4 mol% $AgSbF_6$, 2 mL solvent, 30 μL water when added, room temperature. [b] Determined by ^1H NMR analysis of the crude products. [c] *S* product, determined by HPLC analysis with a chiralpak OD-H column.

2.4 Asymmetric Hydrogenation of Cyclic Imines 6

The applicability of **2** was also demonstrated in the hydrogenation of imine precursors to tetrahydro-β-carbolines. The results are summarized in Table 2-8. Unlike the reduction of **4**, these reactions were performed in methanol. This is because all the substrates **6** have low solubility in DCM but are soluble in methanol. In contrast to the less electron-rich **4a-4d**, all the alkyl substituted imines **6** gave rise to excellent isolated yields and ee's, including those having cyclohexyl and ^{t}Bu groups, although **6e** necessitated a longer time of 12 h.

Table 2-8: Asymmetric hydrogenation of cyclic imines **6** to give amines **7**.[a]

Entry	**6**	substrate	time (h)	yield (%)	ee (%) [b]
1	**6a**		3	95	99
2	**6b**		3	96	99
3	**6c**		3	94	98
4	**6d**		3	95	98
5[c]	**6d**		24	91	98
6	**6e**		12	97	>99
7	**6f**		4	94	99
8	**6g**		3	96	20
9[d]	**6h**		5	95	96
10	**6i**		5	95	99

[a] The conditions were the same as those in Table 2-7 except with MeOH being used as solvent. [b] *S* product. [c] 0.1 mol% **1** and 0.4 mol% $AgSbF_6$ at 50 bar H_2. [d] The ee was determined using a Chiralpak AD column.

Remarkably, the electronic properties of the aryl substituents impact significantly on the enantioselectivity. Thus, in contrast to the *p*-trifluoromethyl substituted **6h**, which led to a 95% ee, the *p*-methoxyl analogue **6g** afforded an ee of only 20%, showing the importance of electronic effects on the process of C=N bond facial discrimination. In line with this trend, when the electronic effect is mitigated with a spacer, a high ee of 99% was obtained (entry 10). Like **6i**, the product **7i** is highly bioactive.[1,3]

Table 2-9 Optimization of conditions for the hydrogenation of **6g**.[a]

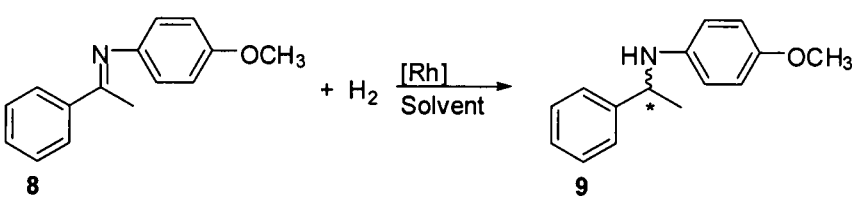
entry	additive	time (h)	pressure H_2 (bar)	solvent	conversion (%) [b]	ee (%)
1	$AgBF_4$	4	20	MeOH	99	11
2	AgOTf	4	20	MeOH	99	9
3	Ag_3PO_4	4	20	MeOH	95	8
4	$AgSbF_6$	4	20	MeOH	99	20
5	$AgSbF_6$	4	20	CH_3CN	5	n.d.
6	$AgSbF_6$	4	20	MeOH/DCM [c]	99	12
7	$AgSbF_6$	4	30	MeOH	99	16
8	$AgSbF_6$	1	20	MeOH	99	20
9 [d]	$AgSbF_6$	4	20	MeOH	99	4
10 [e]	$AgSbF_6$	4	20	MeOH	99	1
11 [f]	$AgSbF_6$	4	20	MeOH	99	10
12 [g]	$AgSbF_6$	4	20	MeOH	99	97

[a] Reaction conditions: 0.5 mmol **6g**, 1 mol% **1** (5 μmol), 4 mol% silver salt, 2 mL solvent, 30 μl H_2O, room temperature. [b] Determined by ^1H NMR analysis of the crude products. [c] 1 ml MeOH and 1 ml DCM. [d] The analogous [Cp*RhCl(CF_3TsCYDN-H)] as catalyst (1 mol% catalyst). [e] The analogous [Cp*RhCl(TsCYDN-H)] as catalyst (1 mol% catalyst). [f] The analogous [Cp*RhCl(CsDPEN-H)] as catalyst (1 mol% catalyst). [g] 1.0 mol% [Cp*IrCl(TsDPEN-H)] as catalyst.

In order to obtain a better ee of **7g**, a range of conditions were explored by optimization of conditions. The screening results are shown in Table 2-9. Although the catalyst **2** afforded only 20% ee of **7g**, it still afforded the best enantioselectivity for hydrogenation of **6g** in comparsion with those catalysts derived from $AgBF_4$, AgOTf or Ag_3PO_4, which led to 11% , 9% and 8% ee, respectively (entries 1-4). Catalyst **2** almost lost activity in the strongly coordinating solvent CH_3CN, which led to only 5% conversion of **7g** in 4 h (entry 5). These solvent and anion effects are consistent with the previous observations. Further more, making the reaction solvent less polar by adding CH_2Cl_2 or increasing the hydrogen pressure somewhat decreased the ee's of **7g** (entries 6 and 7). Further optimizations by changing ionic **2** to the more electron-deficient or rich diamine-ligated analogue [Cp*RhCl(CF_3TsCYDN-H)] or [Cp*RhCl(TsCYDN-H)] have not improved the ee's of **7g** (entries 9 and 10); [Cp*RhCl(CsDPEN-H)] was also inefficient in enantioselectivity for the hydrogenation of **6g** (entry 11). However, a high ee of 97% was obtained by using [Cp*IrCl(TsDPEN-H)] together with $AgSbF_6$ (entry 12).

2.5 Asymmetric Hydrogenation of Acylic Imines

To expand the application of the ionic catalyst, **2** and analogues have also been tested for asymmetric hydrogenation of acyclic imine **8**; the results can be seen in Table 2-10.



8 **9**

Table 2-10: Optimization of conditions for the hydrogenation of **8**.[a]

entry	additive	time (h)	solvent	conversion (%) [b]	ee (%) [c]
1	$AgBF_4$	12	DCM	18	2
2	AgOTf	12	DCM	20	1
3	Ag_3PO_4	12	DCM	10	0
4	$AgSbF_6$	12	DCM	35	3
5	$AgNO_3$	12	DCM	20	0
6	$AgSbF_6$ + acid [d]	12	DCM	20	2
7	$AgBF_4 + H_2O$	12	DCM	22	1
8	$AgSbF_6 + H_2O$	12	DCM	40	2
9	$AgSbF_6 + H_2O$	24	MeOH	65	3
10	$AgSbF_6 + H_2O$	24	toluene	50	3

[a] Reaction conditions: 0.5 mmol **8**, 1 mol% **1** (5 μmol), 4 mol% silver salt, 2 mL solvent, 30 μl H_2O when added, room temperature. [b] Determined by ^1H NMR analysis of the crude products. [c] Determined by HPLC analysis. [d] 5% benzoic acid was added.

Probably owning to the equilibrium of syn/anti isomerisation existing during the reaction, 0-3% ee's were obtained by using **2** or analogues bearing various anions in DCM with or without water. Beside the low ee's obtained, the catalytic system also showed low activities for reduction of the acyclic imine **8**. A 10-35% conversion were recorded by using **1** with $AgBF_4$, AgOTf, Ag_3PO_4, $AgSbF_6$ or $AgNO_3$ in dried DCM (entries 1-5). Furthermore, addition of 5% benzoic acid also could not promote the reduction in the presence of catalyst **2** (entry 6). A slightly improved conversion of 40% was made by using **1** with $AgSbF_6$ in the presence of a small amount of water in

12 h; the maximum conversion reached was 65% by a prolonged time of 24 h. Some of the acyclic imine decomposed to actophenone and *p*-anisidine during the reaction in the presence of water (entries 8 and 9), partly explaining the low yield obtained. However, a lower conversion was observed when the solvent was toluene (entry 10).

3. Conclusion

In conclusion, we have developed a diamine-ligated, ionic Rh(III) catalyst **2** for asymmetric hydrogenation of cyclic imines. The catalyst displayed high activity and excellent enantioselectivity in the reduction of a range of cyclic imines to give bioactive tetrahydroisoquinolines and tetrahydro-β-carbolines. The cationic nature and the bulky non-coordinating counter anion are believed to be the key to the success of **2**.

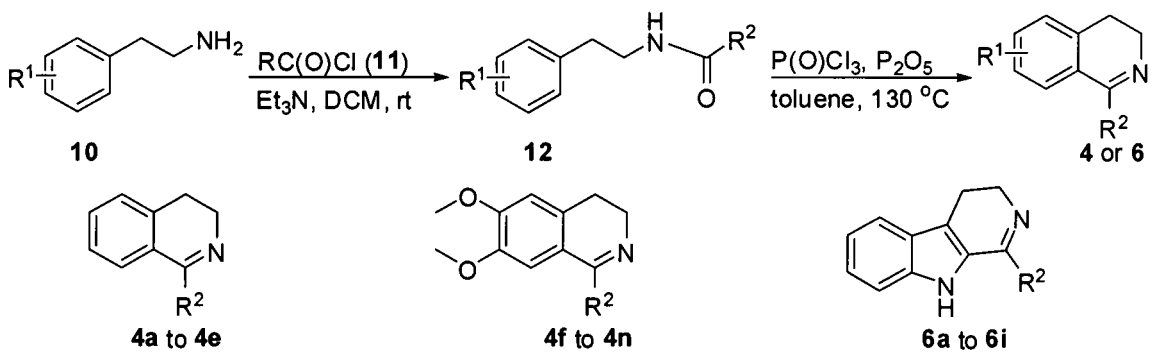
4. Experimental Section

General Infromation

Unless otherwise specified, the chemicals were obtained commercially and used without further purification. The compounds (*R*,*R*)-**1** and (*R*,*R*)-**3** were prepared according to the literature.[20,10a] All the cyclic imines were prepared according to the following procedure, and were characterized by ^{1}H NMR. Dichloromethane (DCM) was dried over CaH_2 and distilled prior to use. Methanol was dried over Mg and distilled prior to use. ^{1}H NMR and ^{13}C NMR spectra were recorded on a DRX-400 spectrometer at 400 (^{1}H) and 100 MHz (^{13}C) in ppm with TMS as the internal standard in $CDCl_3$. The mass spectra were obtained by chemical ionization (CI). Gas

chromatographic analysis was carried out on a Varian 3800 GC equipped with a Beta DEX-120 column and an FID detector. HPLC analysis was performed on Gilson UV/VIS-151 equipped with a Chiralpak AD or Chiralcel OD-H column purchased from Daicel Chemical Industries. Chromatographic purification was performed on silica gel (mesh 300-400) by the flash techinique. All the products were satisfactorily characterized by ^{1}H and ^{13}C NMR, HRMS and element analysis. When possible, comparison of their NMR spectra has been made with available literature data. The configuration of the products **5f**, **5g**, **5h**, **5i**, **5n**, **7a**, **7b**, **7c**, **7d**, and **7f** was assigned by comparison of their HPLC retention times with the literature,[2] and that of the other product was based on analogy with the assignment for other compounds without further verification.

General Procedure for the Preparation of Substrates 4 and 6 [5,21]



Preparation of 12 To a stirred solution of **10** (0.15 mol) in anhydrous CH_2Cl_2 (200 mL) under N_2 was added Et_3N (27.8 mL, 0.20 mol). Freshly distilled **11** (0.16 mol) was added dropwise with stirring. A white precipitate formed immediately, and the reaction mixture was stirred at room temperature overnight. Aqueous NaCl (5%, 200 mL) was

added and following stirring for 0.5 h, CH_2Cl_2 (50 mL) was added. After separation of the CH_2Cl_2 phase, the aqueous layer was extracted with CH_2Cl_2 (100 mL), and the combined organic layer was washed with aqueous NaCl (5%, 2 X 200 mL), dried (Na_2SO_4) and evaporated in vacuo to afford the crude product that was used for next step without any further purification.

Preparation of 4 or **6**. To a three-neck, round-bottom flask under N_2 containing about 0.15 mol of **12** in 500 mL of dry toluene was added P_2O_5 (39.5 g, 0.25 mol) in portions followed by dropwise addition of 41.2 mL (0.44 mol) of freshly of distilled $POCl_3$. The mixture was stirred at reflux under N_2 for 6 h followed by cooling to room temperature, and the toulene were decanted. The solid residue was cooled with an ice bath and cautiously triturated with sufficient 10% NaOH to afford a suspension (pH 8-9). The suspension was extracted with CH_2Cl_2, and the organic extracts dried (Na_2SO_4) and evaporated in vacuo to afford the crude product which was purified by column chromatography. Cyclic imines **4a** to **4n** and **6a** to **6i** were obtained in 45-85% yield.

Complex 2

The compound [Cp*Rh(TsDPEN-H)(H_2O)][SbF_6] **2** was synthesized from **3** and $HSbF_6.6H_2O$ in DCM (TsDPEN-H refers to *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine with the hydrogen on the sulfonylated nitrogen being removed). The isolated complex showed similar activity and selectivity in preliminary studies. Complex **2**: ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.79 (s, 15H,), 2.16 (br, 2H, H_2O), 2.20 (s, 3H), 3.91 (br, 1H), 4.13 (br, 1H),

4.28 (br, 1 H), 4.50 (br, 1H), 6.65-6.69 (m, 2H), 6.79-6.81 (m, 2H), 6.97-7.03 (m, 3H), 7.09 (m, 2H), 7.17-7.23 (m, 5H); MS (ES) for $[C_{31}H_{36}N_2O_2SRh]^+$: *m/z* calcd 603.1553; found 603.1564; Anal. Calcd for $C_{31}H_{36}RhN_2O_2S \cdot H_2O \cdot SbF_6$: C, 43.43; H, 4.47; N, 3.27. Found: C, 43.73; H, 4.41; N, 3.31.

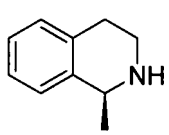
General Procedure for Preparation of Racemic Amines 5 and 7

To a reaction tube charged with a cyclic imine (0.5 mmol) and $NaBH_4$ (1.0 mmol, 38 mg) were added MeOH (2 mL). The readuction was stirred at room temperature for overnight. The solution was transferred to a flask and concentrated to afford the crude product. Flash chromatography purification with a column of silica gel eluted with DCM/MeOH (8/1 to 4/1) yielded the pure product.

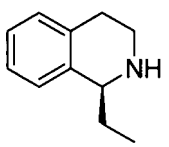
General Procedure for Asymmetric Hydrogenation

To a reaction tube charged with (*R*,*R*)-**1** (3 mg, 5 μmol), $AgSbF_6$ (7 mg, 20 μmol) and a cyclic imine (0.5 mmol) were added DCM (2 mL) and distilled H_2O (30 μL). The reaction tube was put into an autoclave, which was then pressurized with H_2 (20 bar). Following degassing with H_2 three times, the hydrogenation was performed at 20 bar H_2 with stirring at room temperature for a certain period of time. The hydrogen gas was then carefully released, and the solution was transferred to a flask and concentrated to afford the crude product. Flash chromatography purification with a column of silica gel eluted with DCM/MeOH (8/1 to 4/1) yielded the pure product.

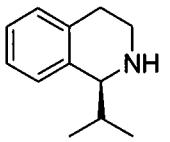
Analytic Data of Products



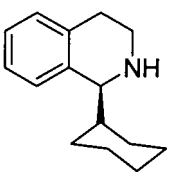
1-Methyl-1,2,3,4-tetrahydroisoquinoline (5a).[22,23] 69 mg obtained (eluent: DCM/MeOH = 6/1-3/1), 94% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.46 (d, J = 6.6 Hz, 3H), 1.71 (br, 1H), 2.78 (dt, J = 4.4 Hz, 16.0 Hz, 1H), 2.84-2.93 (m, 1H), 3.00-3.09 (m, 1H), 3.30 (dt, J = 5.2 Hz, 12.4 Hz, 1H), 4.11 (q, J = 6.4 Hz, 1H), 7.06-7.08 (m, 1H), 7.10-7.16 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 23.1, 30.5, 42.2, 52.0, 126.2, 126.3(2C), 129.6, 135.20, 141.0; HRMS for $C_{10}H_{14}N$ $[M+H]^+$: *m/z* calcd 148.1126, found 148.1127; Elemental analysis calcd (%) for $C_{10}H_{13}N$: C, 81.59; H, 8.90; N, 9.51; Found: C, 81.89; H, 9.12; N, 9.13; GC (Beta DEX-120 column, 110 °C): t_R = 84.0 min (minor), t_S = 85.7 min (major); 99% ee.



1-Ethyl-1,2,3,4-tetrahydroisoquinoline (5b).[24] 76 mg obtained (eluent: DCM/MeOH = 6/1- 4/1), 95% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.01 (t, J = 7.6 Hz, 3H), 1.69-1.80 (m, 1H), 1.88-1.98 (m, 1H), 2.63 (br, 1H), 2.75 (dt, J = 5.2 Hz, 16.4 Hz, 1H), 2.80-2.88 (m, 1H), 2.96-3.02 (m, 1H), 3.25 (dt, J = 5.2 Hz, 12.4 Hz, 1H), 3.92 (dd, J = 3.6 Hz, 8.4 Hz, 1H), 7.06-7.08 (m, 1H), 7.10-7.015 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 10.9, 29.3, 30.3, 41.4, 57.4, 126.2, 126.3, 126.6, 129.6, 135.5, 139.7; HRMS for $C_{11}H_{16}N$ $[M+H]^+$: *m/z* calcd 162.1283, found 162.1286; Elemental analysis calcd (%) for $C_{11}H_{15}N$: C, 81.94; H, 9.38; N, 8.69; Found: C, 81.59; H, 9.25; N, 9.03; HPLC (Chiralcel OD-H, hexane:isopropanol:diethylamine = 99:1:0.1, flow rate 0.5 mL/min, 254 nm): t_S = 18.7 min (major), t_R = 22.8 min (minor); 97% ee.

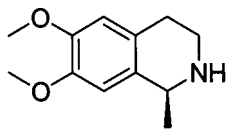


1-Isopropyl-1,2,3,4-tetrahydroisoquinoline (5c).[25] 74 mg obtained (eluent: DCM/MeOH = 6/1- 4/1), 85% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.74 (d, *J* = 7.2 Hz, 3H), 1.11 (d, *J* = 7.2 Hz, 3H), 1.78 (br, 1H), 2.30-2.38 (m, 1H), 2.66 (dt, *J* = 3.2 Hz, 14.8 Hz, 1H), 2.81-2.89 (m, 1H), 2.90-2.96 (m, 1H), 3.27-3.32 (m, 1H), 3.94 (d, *J* = 3.6 Hz, 1H), 7.06-7.11 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 16.1, 20.7, 30.9, 32.5, 42.9, 61.4, 126.0, 126.3, 126.4, 129.6, 136.7, 139.2; HRMS for $C_{12}H_{18}N$ $[M+H]^+$: *m/z* calcd 176.1439, found 176.1441; Elemental analysis calcd (%) for $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99; Found: C, 82.69; H, 10.10; N, 7.63; HPLC (Chiralcel OD-H, hexane:isopropanol: diethylamine = 99:1:0.1, flow rate 0.5 mL/min, 254 nm): t_S = 11.2 min (major), t_R = 12.1 min (minor); 83% ee.

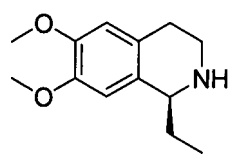


1-Cyclohexyl-1,2,3,4-tetrahydroisoquinoline (5d).[24] 97 mg obtained (eluent: DCM/MeOH = 6/1- 4/1), 90% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.06-1.19 (m, 3H), 1.28-1.42 (m, 3H), 1.65-1.73 (m, 3H), 1.80-1.84 (m, 1H), 1.88-1.92 (m, 1H), 2.15 (br, 1H), 2.65 (dt, *J* = 4.0 Hz, 15.6 Hz, 1H), 2.78-2.86 (m, 1H), 2.88-2.95 (m, 1H), 3.23-3.30 (m, 1H), 3.91 (d, *J* = 4.4 Hz, 1H), 7.04-7.14 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 26.8, 27.0, 27.1, 27.5, 30.7, 31.4, 42.8, 43.4, 61.2, 125.9, 126.0, 126.5, 129.6, 136.7, 138.9; HRMS for $C_{15}H_{22}N$ $[M+H]^+$: *m/z* calcd 216.1752, found 216.1754; Elemental analysis calcd (%) for $C_{15}H_{21}N$: C, 83.67; H, 9.83; N, 6.50; Found: C, 83.69;

H, 10.10; N, 6.63; HPLC (Chiralcel OD-H, hexane:isopropanol: diethylamine = 90:10:0.1, flow rate 0.5 mL/min, 254 nm): t_S =9.4 min (major), t_R = 10.3 min (minor); 91% ee.

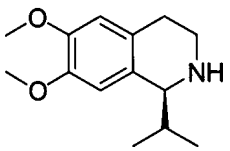


6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (5f).[10a] 98 mg obtained (eluent: DCM/MeOH = 4/1- 1/1), 95% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.43 (d, *J* = 6.8 Hz, 3H), 1.74 (br, 1H), 2.64 (dt, *J* = 4.8 Hz, 16.0 Hz, 1H), 2.75-2.83 (m, 1H), 2.96-3.02 (m, 1H), 3.25 (dt, *J* = 4.8 Hz, 12.4 Hz, 1H), 3.84 (s, 3H), 3.85 (s, 3H), 4.04 (q, *J* = 6.8 Hz, 1 H), 6.57 (s, 1H), 6.63 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 23.3, 30.0, 42.3, 51.6, 56.2, 56.4, 109.4, 112.1, 127.2, 132.9, 147.6; 147.7; HRMS for $C_{12}H_{18}NO_2$ $[M+H]^+$: *m/z* calcd 208.1338, found 208.1342; Elemental analysis calcd (%) for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76; Found: C, 69.69; H, 8.10; N, 6.63; HPLC (Chiralcel OD-H, hexane:isopropanol: diethylamine = 80:20:0.1, flow rate 0.5 mL/min, 280 nm): t_S = 18.0 min (major), t_R = 23.9 min (minor); 96% ee.

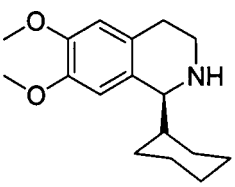


6,7-Dimethoxy-1-ethyl-1,2,3,4-tetrahydroisoquinoline (5g).[10a] 104 mg obtained (eluent: DCM/MeOH = 4/1- 1/1), 94% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.01 (t, *J* = 7.6 Hz, 3H), 1.64-1.76 (m, 1H), 1.78 (br, 1H), 1.85-1.95 (m, 1H), 2.65 (dt, *J* = 5.6 Hz, 16.0 Hz, 1H), 2.71-2.78 (m, 1H), 2.93-2.99 (m, 1H), 3.22 (dt, *J* = 5.6 Hz, 12.0 Hz, 1H), 3.82 (d, J = 2.8 Hz, 1 H), 3.84 (s, 6H), 6.57 (s, 1H), 6.62 (s, 1H); ^{13}C

NMR ($CDCl_3$, 100 MHz) δ (ppm): 10.9, 29.5, 30.0, 41.6, 56.2, 56.4, 57.1, 109.7, 112.2, 127.7, 131.9, 147.5, 147.6; HRMS for $C_{13}H_{20}NO_2$ $[M+H]^+$: *m/z* calcd 222.1494, found 222.1496; Elemental analysis calcd (%) for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33; Found: C, 70.69; H, 8.76; N, 6.66; HPLC (Chiralcel OD-H, hexane:isopropanol: diethylamine = 80:20:0.1, flow rate 0.5 mL/min, 290 nm): t_S = 15.7 min (major), t_R = 20.8 min (minor); 93% ee.

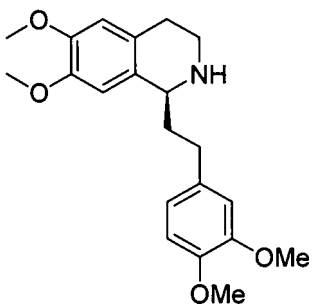


6,7-Dimethoxy-1-isopropyl -1,2,3,4-tetrahydroisoquinoline (5h).[10a] 112 mg obtained (eluent: DCM/MeOH = 6/1- 4/1), 95% yield; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.74 (d, *J* = 6.8 Hz, 3H), 1.12 (d, *J* = 6.8 Hz, 3H), 1.89 (br, 1H), 2.26-2.34 (m, 1H), 2.58 (dt, *J* = 3.6 Hz, 15.6 Hz, 1H), 2.74-2.82 (m, 1H), 2.87-2.94 (m, 1H), 3.26-3.31 (m, 1H), 3.84 (s, 3H), 3.85 (s, 3H), 3.89 (d, *J* = 4.0 Hz, 1 H), 6.57 (s, 1H), 6.65 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 16.0, 20.6, 30.3, 32.8, 43.1, 56.2, 56.4, 61.0, 109.4, 112.1, 128.8, 131.0, 147.4, 147.6; HRMS for $C_{14}H_{22}NO_2$ $[M+H]^+$: *m/z* calcd 236.1651, found 236.1643; Elemental analysis calcd (%) for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95; Found: C, 71.88; H, 9.16; N, 5.76; HPLC (Chiralcel OD-H, hexane:isopropanol: diethylamine = 90:10:0.1, flow rate 0.5 mL/min, 280 nm): t_S = 17.0 min (major), t_R = 21.0 min (minor); 93% ee.



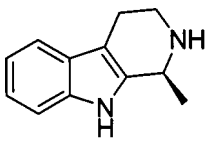
6,7-Dimethoxy-1-cyclohexyl-1,2,3,4-tetrahydroisoquinoline (5i).[9b] 129 mg obtained

(eluent: DCM/MeOH = 6/1-4/1), 94% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.05-1.18 (m, 3H), 1.30-1.43 (m, 3H), 1.66-1.72 (m, 3H), 1.81-1.88 (m, 2H), 2.57 (dt, J = 4.0 Hz, 15.6 Hz, 1H), 2.71-2.79 (m, 1H), 2.86-2.93 (m, 1H), 3.26 (dt, J = 3.6 Hz, 12.0 Hz, 1H), 3.84 (s, 4H, overlapped with NCH), 3.85 (s, 3H), 6.56 (s, 1H), 6.64 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 26.8, 27.0, 27.1, 27.4, 30.2, 31.3, 42.8, 43.6, 56.2, 56.5, 60.7, 109.7, 112.1, 128.8, 130.7, 147.4, 147.5; HRMS for $C_{17}H_{26}NO_2$ $[M+H]^+$: *m/z* calcd 276.1964, found 276.1957; Elemental analysis calcd (%) for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09; Found: C, 74.46; H, 9.23; N, 4.88; HPLC (Chiralcel OD-H, hexane:isopropanol: diethylamine = 90:10:0.1, flow rate 0.5 mL/min, 274 nm): t_S = 17.1 min (major), t_R = 21.1 min (minor); 95% ee.

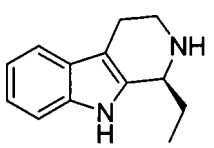


1-(3,4-Dimethoxyphenethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (5n).[22] 170 mg obtained (eluent: DCM/MeOH = 4/1- 1/1), 95% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.90-2.09 (m, 2H), 2.15 (br, 1H), 2.56-2.75 (m, 4H), 2.89-2.95 (m, 1H), 3.17 (dt, J = 5.6 Hz, 12.8 Hz, 1H), 3.75 (s, 3H), 3.77 (s, 3H), 3.78 (s, 3H), 3.79 (s, 3H), 3.90 (dd, J = 3.6 Hz, 8.8 Hz 1H), 6.49 (s, 1H), 6.50 (s, 1H), 6.68-6.74 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 29.8, 32.5, 38.8, 41.5, 55.5(2C), 56.2, 56.3, 56.5, 109.6, 111.7, 112.2, 112.2, 120.6, 127.7, 131.6, 135.4, 147.6, 147.7, 147.8, 149.3; HRMS for $C_{21}H_{28}NO_4$ $[M+H]^+$: *m/z* calcd 358.2018, found 358.2011; Elemental

analysis calcd (%) for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92; Found: C, 70.44; H, 7.77; N, 3.87; HPLC (Chiralcel OD-H, hexane:isopropanol: diethylamine = 60:40:0.1, flow rate 0.5 mL/min, 274 nm): t_S = 27.5 min (major), t_R = 46.3 min (minor); 99% ee.

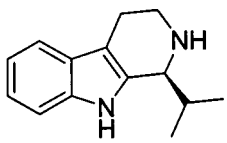


1-Methyl-1,2,3,4-tetrahydro-1*H*-pyrido[3,4-b]indole (7a).[10a] 88 mg obtained (eluent: DCM/MeOH = 4/1- 1/1), 95% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.44 (d, *J* = 6.8 Hz, 3H), 1.96 (br, 1H), 2.67-2.81 (m, 2H), 3.01-3.08 (m, 1H), 3.36 (dt, *J* = 4.4, 12.8 Hz, 1H), 4.17 (q, *J* = 6.8 Hz, 1H), 7.07-7.16 (m, 2H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.97 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 21.1, 23.1, 43.1, 48.7, 108.9, 111.2, 118.5, 119.8, 122.0, 127.9, 136.1, 137.4; HRMS for $C_{12}H_{15}N_2$ $[M+H]^+$: *m/z* calcd 187.1235, found 187.1242; Elemental analysis calcd (%) for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04; Found: C, 77.46; H, 7.88; N, 14.83; HPLC (Chiralcel OD-H, hexane:isopropanol: diethylamine = 80:20:0.1, flow rate 0.5 mL/min, 280 nm): t_R = 25.3 min (minor), t_S = 35.7 min (major); 99% ee.

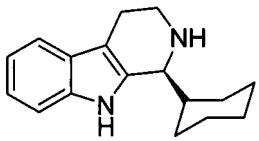


1-Ethyl-1,2,3,4-tetrahydro-1*H*-pyrido[3,4-b]indole (7b).[10a] 100 mg obtained (eluent: DCM/MeOH = 6/1- 4/1), 96% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.02 (t, *J* = 7.6 Hz, 3H), 1.62-1.70 (m, 1H), 1.79 (br, 1H), 1.83-1.93 (m, 1H), 2.68-2.79 (m, 2H), 2.97-3.04 (m, 1H), 3.35 (dt, *J* = 4.4, 12.8 Hz, 1H), 3.95-3.98 (m, 1H), 7.06-7.15 (m, 2H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 8.07 (br, 1H); ^{13}C NMR

($CDCl_3$, 100 MHz) δ (ppm): 10.7, 23.2, 28.1, 43.1, 54.3, 109.5, 111.2, 118.5, 119.7, 121.9, 128.0, 136.1, 136.7; HRMS for $C_{13}H_{17}N_2$ $[M+H]^+$: *m/z* calcd 201.1392, found 201.1396; Elemental analysis calcd (%) for $C_{13}H_{16}N_2$: C, 77.96; H, 8.05; N, 13.99; Found: C, 77.84; H, 8.24; N, 13.88; HPLC (Chiralcel OD-H, hexane:isopropanol: diethylamine = 90:10:0.1, flow rate 0.5 mL/min, 280 nm): t_S = 35.8 min (major), t_R = 50.5 min (minor); 99% ee.

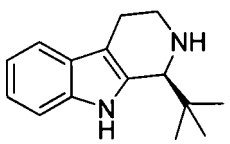


1-Isopropyl-1,2,3,4-tetrahydro-1*H*-pyrido[3,4-b]indole (**7c**).[10a] 101 mg obtained (eluent: DCM/MeOH = 6/1- 4/1), 94% yield; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.86 (d, *J* = 6.80 Hz, 3H), 1.13 (d, *J* = 6.80 Hz, 3H), 1.62 (br, 1H), 2.13-2.21 (m, 1H), 2.68-2.79 (m, 2H), 2.94-3.01 (m, 1H), 3.39 (dt, *J* = 4.0 Hz, 12.4 Hz, 1H), 3.99 (dd, *J* = 2.0 Hz, 4.0 Hz, 1H), 7.07-7.16 (m, 2H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.89 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 17.3, 20.0, 23.2, 32.1, 43.7, 58.6, 110.6, 111.1, 118.4, 119.7, 121.8, 128.0, 136.0, 136.1; HRMS for $C_{14}H_{19}N_2$ $[M+H]^+$: *m/z* calcd 215.1548, found 215.1547; Elemental analysis calcd (%) for $C_{14}H_{18}N_2$: C, 78.46; H, 8.47; N, 13.07; Found: C, 78.78; H, 8.49; N, 12.77; HPLC (Chiralcel OD-H, hexane:isopropanol: diethylamine = 90:10:0.1, flow rate 0.5 mL/min, 290 nm): t_S = 24.7 min (major), t_R = 41.9 min (minor); 98% ee.

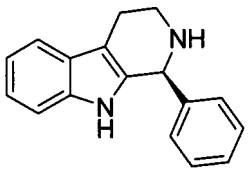


1-Cyclohexyl-1,2,3,4-tetrahydro-1*H*-pyrido[3,4-b]indole (**7d**).[10a] 121 mg obtained

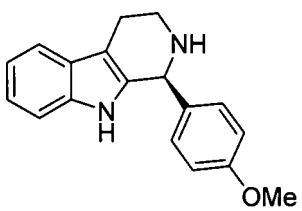
(eluent: DCM/MeOH = 6/1- 4/1), 95% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.08-1.50 (m, 6H), 1.66-1.83 (m, 6H, overlapped with *H*NCH_2), 2.69-2.73 (m, 2H), 2.93-3.00 (m, 1H), 3.36 (dt, *J* = 4.2 Hz, 12.4 Hz, 1H), 3.94 (t, *J* = 1.6 Hz, 1H), 7.06-7.15 (m, 2H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.99 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 23.2, 26.9, 27.1, 27.3, 27.9, 30.7, 42.7, 43.6, 58.3, 110.4, 111.1, 118.4, 119.7, 121.8, 128.0, 135.8, 136.1; HRMS for $C_{17}H_{23}N_2$ $[M+H]^+$: *m/z* calcd 255.1861, found 255.1860; Elemental analysis calcd (%) for $C_{17}H_{22}N_2$: C, 80.27; H, 8.72; N, 11.01; Found: C, 79.98; H, 8.86; N, 11.23; HPLC (Chiralcel OD-H, hexane:isopropanol: diethylamine = 90:10:0.1, flow rate 0.5 mL/min, 280 nm): t_S = 21.4 min (major), t_R = 41.4 min (minor); 98% ee.



1-*tert*-Butyl-1,2,3,4-tetrahydro-1*H*-pyrido[3,4-b]indole (7e). 111 mg obtained (eluent: DCM/MeOH = 6/1- 4/1), 97% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.07 (s, 9H), 1.62 (br, 1H), 2.67-2.70 (m, 2H), 2.86 (dt, *J* = 6.8 Hz, 12.4 Hz, 1H), 3.34 (dt, *J* = 4.0 Hz, 12.4 Hz, 1H), 3.80 (s, 1H), 7.06-7.15 (m, 2H), 7.28 (d, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 8.0 Hz 1H), 7.80 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 23.6, 27.9, 36.3, 44.0, 62.9, 111.1, 112.3, 118.4, 119.7, 122.0, 127.7, 135.1, 136.1; HRMS for $C_{15}H_{21}N_2$ $[M+H]^+$: *m/z* calcd 229.1705, found 229.1708; Elemental analysis calcd (%) for $C_{15}H_{20}N_2$: C, 78.90; H, 8.83; N, 12.27; Found: C, 79.00; H, 8.86; N, 11.99; HPLC (Chiralcel OD-H, hexane:isopropanol: diethylamine = 90:10:0.1, flow rate 0.5 mL/min, 280 nm): t_S = 21.4 min (major), t_R = 38.8 min (minor); >99% ee.

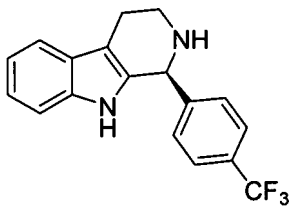


1-Phenyl-1,2,3,4-tetrahydro-1*H*-pyrido[3,4-b]indole (7f).[10a] 117 mg obtained (eluent: DCM/MeOH = 6/1- 4/1), 94% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.78 (br, 1H), 2.73-2.79 (m, 1H), 2.82-2.90 (m, 1H), 2.99-3.06 (m, 1H), 3.24 (dt, *J* = 4.8 Hz, 12.8 Hz, 1H), 5.01 (s, 1H), 7.06-7.09 (m, 3H), 7.18-7.22 (m, 2H), 7.26-7.30 (m, 3H), 7.49-7.52 (m, 1H), 8.00 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 22.9, 43.2, 58.5, 110.6, 111.3, 118.7, 119.8, 122.1, 127.8, 128.6, 129.0, 129.2, 134.9, 136.3, 142.3; HRMS for $C_{17}H_{17}N_2$ $[M+H]^+$: *m/z* calcd 249.1392, found 249.1398; Elemental analysis calcd (%) for $C_{17}H_{16}N_2$: C, 82.22; H, 6.49; N, 11.28; Found: C, 82.00; H, 6.88; N, 11.02; HPLC (Chiralcel OD-H, hexane:isopropanol: diethylamine = 80:20:0.1, flow rate 0.5 mL/min, 280 nm): t_S = 25.6 min (major), t_R = 40.4 min (minor); 99% ee.

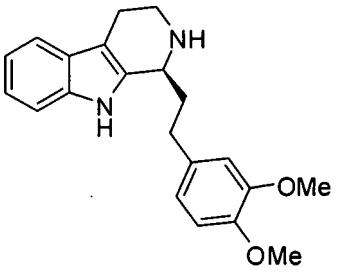


1-(4-Methoxyphenyl)-1,2,3,4-tetrahydro-1*H*-pyrido[3,4-b]indole (7g). 133 mg obtained (eluent: DCM/MeOH = 6/1- 4/1), 96% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.77 (br, 1H), 2.72-2.79 (m, 1H), 2.82-2.90 (m, 1H), 2.99-3.06 (m, 1H), 3.26 (dt, *J* = 4.4 Hz, 12.4 Hz, 1H), 3.74 (s, 3H), 4.99 (s, 1H), 6.80 (d, *J* = 8.4 Hz, 2H), 7.05-7.14 (m, 5H), 7.49-7.52 (m, 1H), 8.03 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 22.9, 43.1, 55.8, 57.8, 110.5, 111.3, 114.5, 118.6, 119.7, 122.0, 127.8, 130.1, 134.4, 135.3, 136.3, 159.9; HRMS for $C_{18}H_{19}N_2O$ $[M+H]^+$: *m/z* calcd 279.1497, found

279.1497; Elemental analysis calcd (%) for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06; Found: C, 77.93; H, 6.73; N, 10.00; HPLC (Chiralcel OD-H, hexane:isopropanol: diethylamine = 80:20:0.1, flow rate 0.5 mL/min, 280 nm): t_S = 33.2 min (major), t_R = 48.6 min (minor); 97% ee.



1-(4-Trifluorophenyl)-1,2,3,4-tetrahydro-1*H*-pyrido[3,4-b]indole (7h). 150 mg obtained (eluent: DCM/MeOH = 6/1- 4/1), 95% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.95 (br, 1H), 2.84-2.90 (m, 1H), 2.92-3.00 (m, 1H), 3.13-3.19 (m, 1H), 3.33 (dt, J = 4.8 Hz, 12.4 Hz, 1H), 5.17 (s, 1H), 7.15-7.23 (m, 3H), 7.42 (d, J = 8.0 Hz, 2H), 7.59-7.64 (m, 3H), 7.83 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 22.9, 42.9, 57.90, 111.0, 111.3, 118.7, 120.0, 122.5, 124.5 (q, J_{CF} = 270.6 Hz), 126.2 (q, J_{CF} = 3.8 Hz), 127.7, 129.4, 130.9 (q, J_{CF} = 32.4 Hz), 133.7, 136.4, 146.3; HRMS for $C_{18}H_{16}F_3N_2$ $[M+H]^+$: *m/z* calcd 317.1266, found 317.1265; Elemental analysis calcd (%) for $C_{18}H_{15}F_3N_2$: C, 68.35; H, 4.78; N, 8.86; Found: C, 68.74; H, 4.70; N, 8.58; HPLC (Chirapak AD, hexane:isopropanol: diethylamine = 80:20:0.1, flow rate 0.5 mL/min, 280 nm): t_R = 14.2 min (minor), t_S = 19.8 min (major); 96% ee.



1-(3,4-Dimethoxyphenethyl)-1,2,3,4-tetrahydro-1*H*-pyrido[3,4-b]indole (7i). 160

mg obtained (eluent: DCM/MeOH = 4/1- 1/1), 95% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.74 (br, 1H), 1.95-2.03 (m, 1H), 2.11-2.19 (m, 1H), 2.70-2.87 (m, 4H), 3.02-3.09 (m, 1H), 3.34-3.39 (m, 1H), 3.84 (s, 3H), 3.85 (s, 3H), 4.10-4.13 (m, 1H), 6.74-6.81(m, 3H), 7.07-7.16 (m, 2H), 7.25-7.28 (m, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.73 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 23.2, 32.2, 37.4, 42.9, 52.6, 56.3, 56.4, 109.6, 111.1, 111.8, 112.2, 118.5, 119.8, 120.6, 122.0, 127.9, 134.9, 136.1, 136.4, 147.8, 149.4; HRMS for $C_{21}H_{25}N_2O_2$ $[M+H]^+$: *m/z* calcd 337.1916, found 337.1908; Elemental analysis calcd (%) for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33; Found: C, 75.23; H, 7.31; N, 8.11; HPLC (Chiralcel OD-H, hexane:isopropanol: diethylamine = 60:40:0.1, flow rate 1.0 mL/min, 280 nm): t_R = 17.5 min (minor), t_S = 44.2 min (major); 99% ee.

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section)

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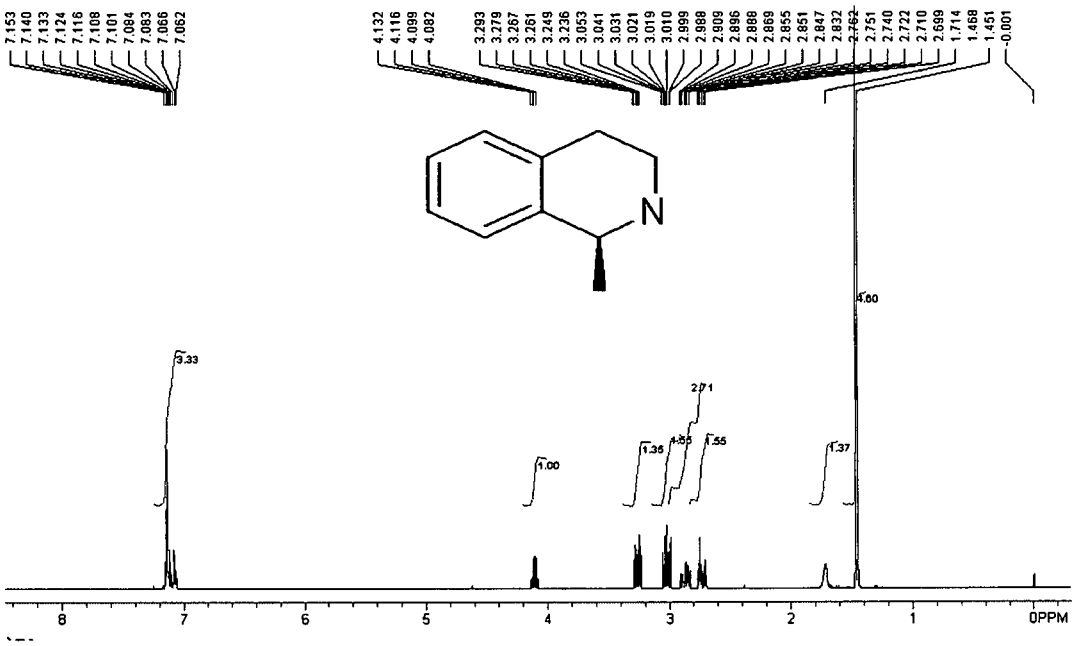
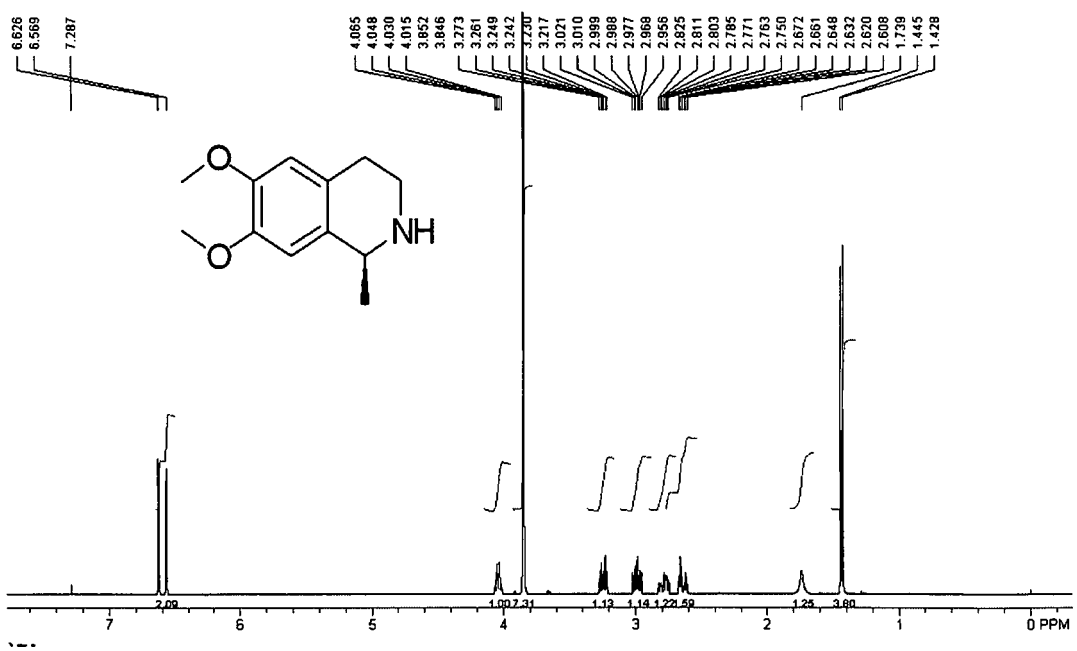
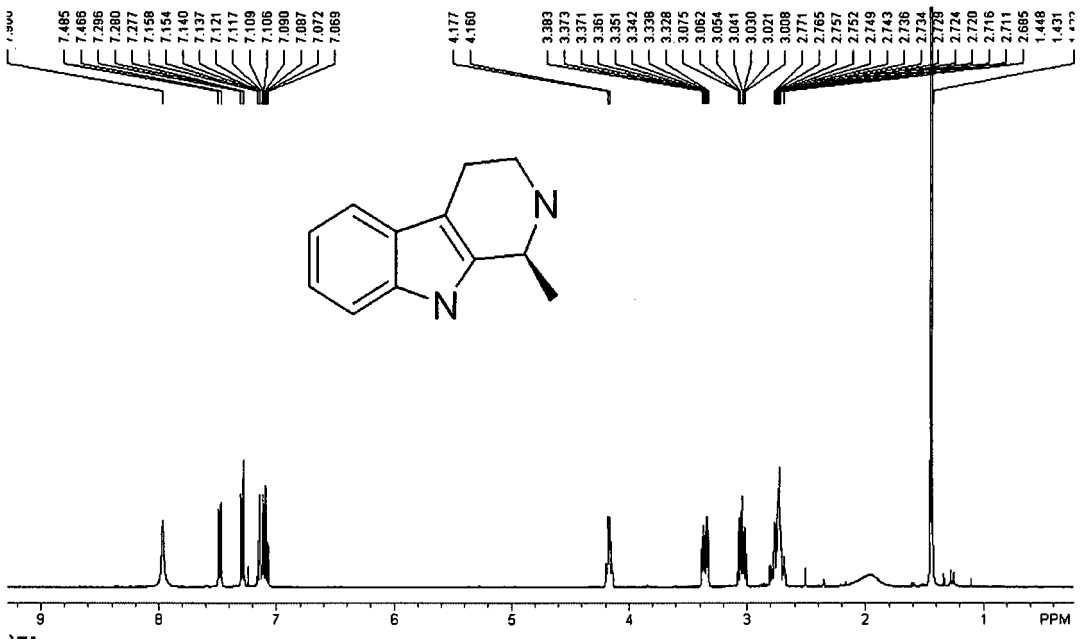
6. ^{1}H NMR Spectra (400 MHz, $CDCl_3$)



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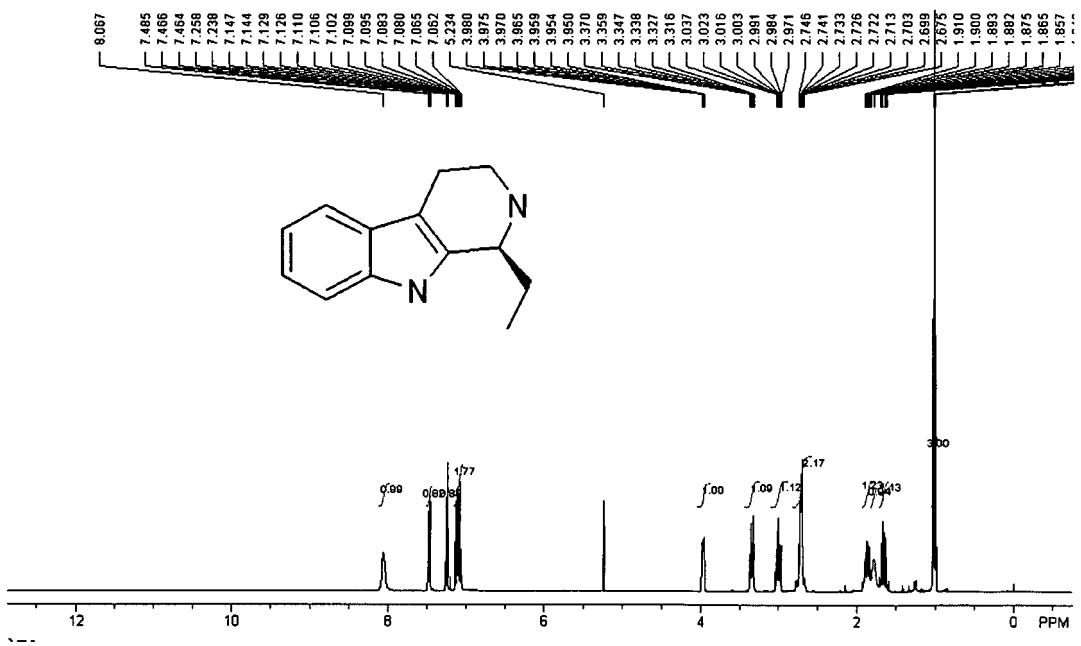
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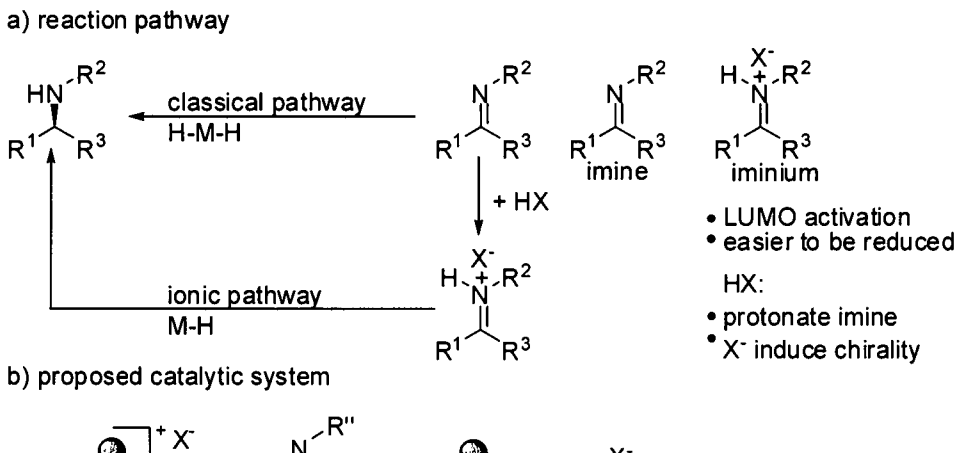
Chapter 3. Chiral Counter Anion-Aided Asymmetric Hydrogenation of Acyclic Imines

1. Introduction

Asymmetric hydrogenation of imines provides direct access to chiral amines, one of the most important functionalities in fine chemical, agrochemical and pharmaceutical products.[1,2] However, in terms of both enantioselectivity and substrate scope, this transformation remains challenging, particularly in the case of acyclic imines.[1b,c] The vast majority of the transition metal catalysts reported thus far employ phosphorus-containing ligands, and it is generally believed that the reduction proceeds via imine nitrogen coordination to the metal center.[1c] However, Norton recently showed that imines can be reduced through an ionic pathway, where a Ru(II)-H_2 complex is deprotonated by an amine and the resulting Ru(II)-H reduces preformed iminium salts (Scheme 3-1a).[3] In more recent studies in organocatalysis,[4] the groups of Rueping, List, and MacMillan reported highly enantioselective transfer hydrogenation with Hantzsch ester of imines[4b,c] or imines in situ generated from ketones and amines;[4d] the reduction is catalyzed by chiral phosphoric acids, which protonate the imines while the anion of which directs the facial attack of the hydride (Scheme 3-1a). Inspired by these discoveries, we envisioned that if a heterolitically hydrogen-activating catalyst[5] is associated with a chiral counter anion, the latter may be exploited to influence the enantiodiscrimination of the chiral ligands by ion-paring with the resulting iminium cation (Scheme 3-1b).[6] In this chapter, we show that when combined with a chiral phosphate anion, chiral diamine-ligated Ir(III) catalysts indeed

enable highly enantioselective asymmetric hydrogenation of acyclic imines, affording up to 99% ee. To broaden the concept of counter anion-aided catalysis, the combination of various achiral (chiral) acids with different chiral (achiral) transition metal catalysts have also been investigated for enantioselective hydrogenation of the model imine 4-methoxy-*N*-(1-phenylethylidene)benzenamine **1a**, affording the amine with up to 73% ee.



Scheme 3-1. Reduction of imines via ionic pathway.

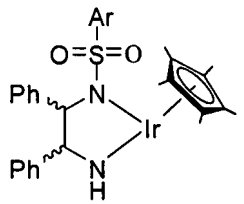
2 Results and Discussion

2.1 Chiral Diamine-ligated Ir(III) and Chiral Anion System

We have found that the complex [Cp*Rh(TsDPEN-H)(H_2O)][SbF_6] acts as an excellent catalyst for asymmetric hydrogenation of cyclic imines; that is described in Chapter 2.[7-9] However, disappointing results were obtained with acyclic imines. Thus,

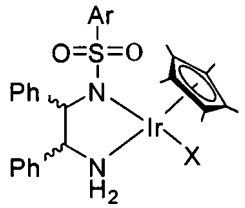
in the reduction of the model imine **1a** at 20 bar H_2 in toluene, an ee of only 3% was observed at 20 °C (Table 3-1, entry 1). In contrast, the analogous Ir(III) complex or (*S*, *S*)-**3a** with 6% $HSbF_6$ led to encouraging results, affording a 22%-26% ee (entries 2 and 3). This prompted us to search for Cp*Ir(III) catalysts containing chiral anions, such as chiral carbonate sulfate and phosphate anion. A quick way for accessing such catalysts is to protonate the 16e complex **3** with the corresponding commercially available chiral acids, e.g. L-proline, (*R*) or (*S*)-camphor-10-sulfonic acids (CSA), or easily prepared phosphoric acid **5**,[10] which are expected to in situ generate the catalyst **4** or analogues.[11] As can be seen from Table 3-1, **3a** was inactive in hydrogenating **1a** (entry 4). To our surprise, the combination of **3a** and L-proline also was inactive for the hydrogenation of **1a** (entry 5); and the combination of **3a** with *R*-CSA or *S*-CSA afforded the amine with the same configuration in 7% ee and 91% conversion or 12% ee and 94% conversion (entries 6-7). The results indicate that L-proline, containing both an acid and amine functional group, may not protonate the 16e **3a** to form the analogue of **4** and the less bulky *R*-CSA or *S*-CSA could not aid **4** to induce chirality in the hydrogenation. Changing the anion to the phosphate **5**, the combination of **3a** and **5a-e** delightfully led to good conversions and enantioselectivities, which vary with the phosphoric acid used, with **5e** promoting an excellent ee of 97% (entry 12). The **3b-5e** and **3c-5e** couples were less enantioselective, however (entries 13 and 14). Remarkably, the phosphoric acids **5a,b** afforded the amine with configuration opposite to that observed with **5c-e** (entries 8-9 vs 10-12), revealing the directing effect of phosphates on enantioselection. Still further, on changing the chirality of the diamine ligand, i.e.

from (*S,S*)-**3a,c** to (*R,R*)-**3a,c**, a dramatic decrease in ee's (entries 12, 14 vs 15, 16) was recorded, showing the chirality of the catalyst needs to match that of its counter anion.



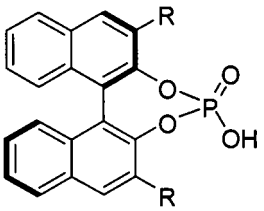
3

a: Ar = 2,4,6-(2-C_3H_7)$_3C_6H_2$
b: Ar = 2,3,4,5,6-$(CH_3)_5C_6$
c: Ar = 4-$CH_3C_6H_4$



4

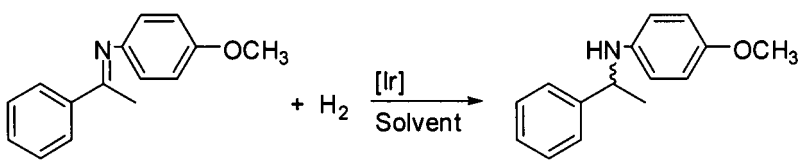
a: Ar = 2,4,6-(2-C_3H_7)$_3C_6H_2$ X = **5e**-H
b: Ar = 2,3,4,5,6-$(CH_3)_5C_6$ X = **5e**-H



5

a: R = H; **b**: R = Ph
c: R = 3,5-$(CF_3)_2C_6H_3$
d: R = 1-naphthyl
e: R = 2,4,6-(2-C_3H_7)$_3C_6H_2$

Table 3-1: Optimization of Conditions for the Hydrogenation of **1a**[a]



1a **2a**

entry	solvent	catalyst	additive	conv. (%)[b]	ee (%)[c]
1	toluene	*cat*[d]	*none*	43	3(*S*)
2	toluene	*cat*[e]	*none*	36	26(*S*)
3	toluene	(*S,S*)-**3a**	$HSbF_6$ (6%)	37	22(*S*)
4	toluene	(*S,S*)-**3a**	*none*	0	-
5	toluene	(*S,S*)-**3a**	L-proline (6%)	0	-
6	toluene	(*S,S*)-**3a**	*R*-CSA	91	7(*S*)
7	toluene	(*S,S*)-**3a**	*S*-CSA	94	12 (*S*)
8	toluene	(*S,S*)-**3a**	**5a** (6%)	53	17(*R*)
9	toluene	(*S,S*)-**3a**	**5b** (6%)	57	26(*R*)
10	toluene	(*S,S*)-**3a**	**5c** (6%)	40	20(*S*)
11	toluene	(*S,S*)-**3a**	**5d** (6%)	43	38(*S*)
12	toluene	(*S,S*)-**3a**	**5e** (6%)	60	97(*S*)
13	toluene	(*S,S*)-**3b**	**5e** (6%)	76	92(*S*)

14	toluene	(*S*,*S*)-**3c**	**5e** (6%)	30	81(*S*)
15	toluene	(*R*,*R*)-**3a**	**5e** (6%)	47	38(*R*)
16	toluene	(*R*,*R*)-**3c**	**5e** (6%)	27	3(*R*)
17	toluene	(*S*,*S*)-**4a**	*none*	76	97(*S*)
18	toluene	(*S*,*S*)-**4a**	**5e** 0.5%)	90	97(*S*)
19	toluene	(*S*,*S*)-**4a**	**5e** (1%)	92	97(*S*)
20	toluene	(*S*,*S*)-**4a**	**5e** (3%)	84	97(*S*)
21	toluene	(*S*,*S*)-**4a**	**5e** (7%)	69	96(*S*)
22	toluene	(*S*,*S*)-**4a**	**5e** (10%)	60	96(*S*)
23	DCM	(*S*,*S*)-**4a**	**5e** (1%)	88	94(*S*)
24	Benzene	(*S*,*S*)-**4a**	**5e** (1%)	93	97(*S*)
25	CH_3CN	(*S*,*S*)-**4a**	**5e** (1%)	9	10(*S*)
26	THF	(*S*,*S*)-**4a**	**5e** (1%)	60	92(*S*)
27	methanol	(*S*,*S*)-**4a**	**5e** (1%)	18	8(*S*)
28[f]	toluene	(*S*,*S*)-**4a**	**5e** (5%)	83	99(*S*)

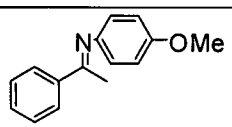
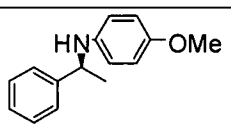
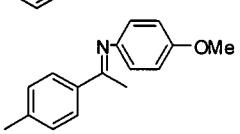
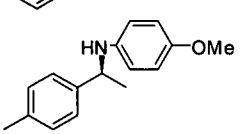
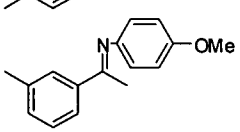
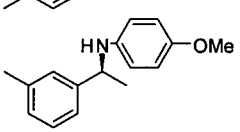
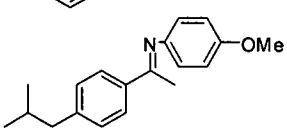
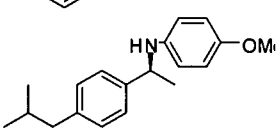
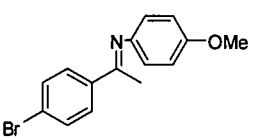
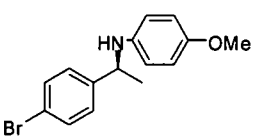
[a] Reaction conditions: 0.5 mmol **1a**, 1 mol% catalyst, 2 mL solvent, 20 bar H_2, 20 °C, 12 h. [b] Determined by ^1H NMR analysis of the crude product. [c] Determined by HPLC analysis; configuration assigned by comparison with the literature.[2,4] [d] 1 mol% [Cp*Rh(TsDPEN-H)(H_2O)][SbF_6]. [e] 1 mol% [Cp*Ir(TsDPEN-H)(H_2O)][SbF_6]. [f] 10 °C, 18 h.

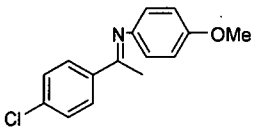
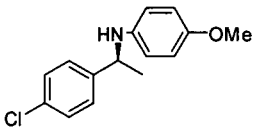
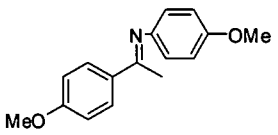
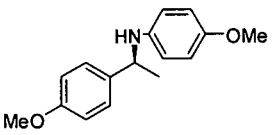
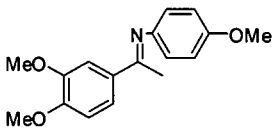
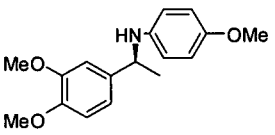
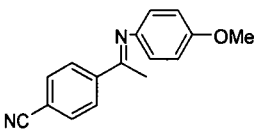
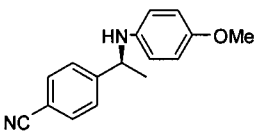
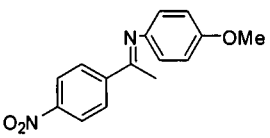
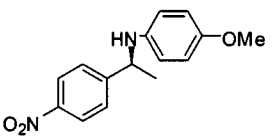
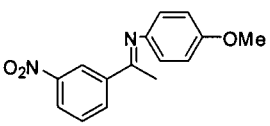
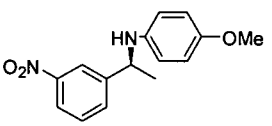
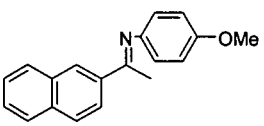
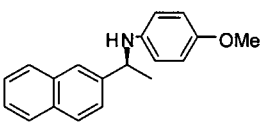
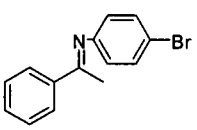
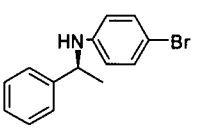
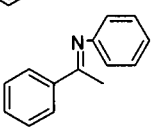
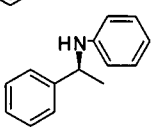
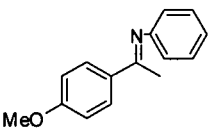
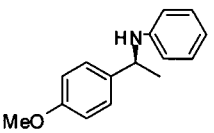
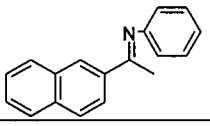
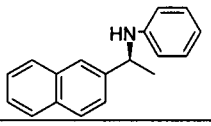
Having identified the bulky **5e** to be the best promoter for enantioselectivity amongst **5a-e**, we prepared the complex **4a**, which has the conjugate base of **5e** as the counter anion. Using **4a** as catalyst with no additional phosphoric acid, the hydrogenation of **1a** afforded the same ee as when the catalyst was in situ prepared from **3a** and **5e** (entries 12 vs.17). Introduction of more acid **5e** was found to increase the reaction rate probably by increasing the concentration of iminium salt (entries 17-19). However, additional **5e** was found to decrease the catalytic activity, with the highest conversion

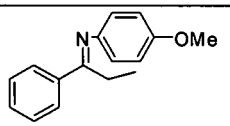
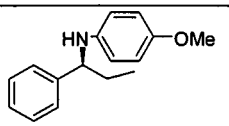
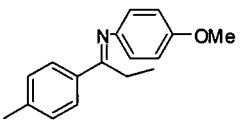
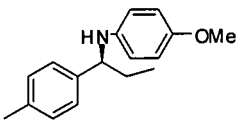
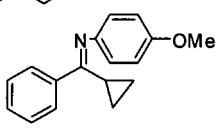
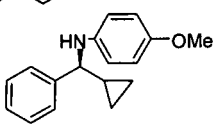
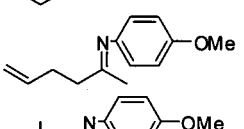
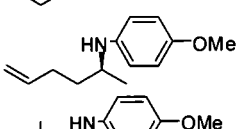
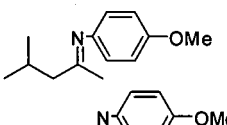
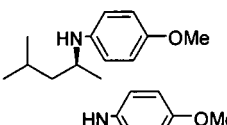
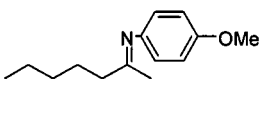
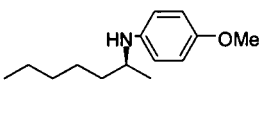
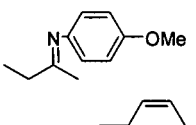
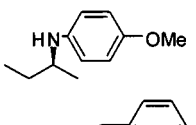
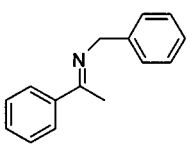
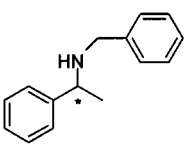
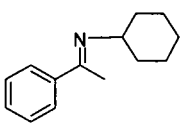
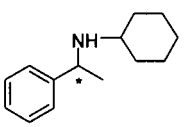
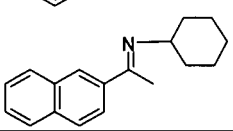
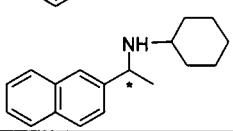
being observed at ca 1 mol% **5e** (entries 18-22), probably because the additional **5e** might destroy the active catalyst thus decreasing the concentration of the catalyst in solution. A higher ee of 99% was obtained when the hydrogenation was performed at a lower temperature of 10 °C (entry 28). As with reactions that involve ion-pairing intermediates,[6] the hydrogenation is solvent sensitive. Thus, lower ee's and conversion were observed in more polar solvents such as THF (92% ee, 60% conversion), MeCN (10% ee, 9% conversion) and methanol (8% ee, 18% conversion) (entries 25-27).

Using the optimized conditions, i.e. 1 mol% **4a** or the analogous **4b** in the presence of 1 mol% **5e**, a range of acyclic imines were hydrogenated. The results are given in Table 3-2.

Table 3-2. Asymmetric Hydrogenation of Imines **1** to Amines **2**[a]

entry	**1**	substrate	product	time (h)	yield (%)[b]	ee (%)[c]
1	**1a**			15	94	97
2	**1b**			15	93	97
3	**1c**			15	95	96
4	**1d**			15	94	98
5	**1e**			15	93	97

6	**1f**			15	94	96
7	**1g**			15	93	97
8	**1h**			15	92	97
9	**1i**			20	94	93
10	**1j**			20	93	92
11	**1k**			20	93	84
12	**1l**			15	96	98
13	**1m**			15	93	94
14	**1n**			15	94	95
15	**1o**			15	93	97
16	**1p**			15	94	95

17[d]	**1q**			15	92	90
18[d]	**1r**			15	93	91
19[d]	**1s**			15	92	97
20[d]	**1t**			15	88	95
21[d,e]	**1u**			15	90	92
22[d,e]	**1v**			15	91	94
23[d,e]	**1w**			15	88	91
24[f]	**1x**			24	4	-
25[f]	**1y**			24	0	-
26[f]	**1z**			24	0	-

[a] Reaction conditions: 0.5 mmol **1a**, 1 mol% **4a**, 1 mol% **5e**, 2 mL toluene, 20 bar H_2, 20 °C, 15-20 h. [b] Isolated yields. [c] Determined by HPLC analysis; *S* configuration, assigned by comparison with the literature.[2,4d] (*S*,*S*)-**4b** as catalyst. With **4a**, the ee's were ca 6% lower. [e] Configuration was assigned by analogy with entry 20. [f] (*S*,*S*)-**4a** with 1 mol%, 3 mol%, 5 mol% and 10 mol% **5e** were used for hydrogenation at 20 °C or 50 °C; similar results were obtained or with (*S*,*S*)-**4b**.

As can be seen, a wide spectrum of imines are hydrogenated with **4**, affording excellent yields and ee's with almost all the *N*-aryl imines. Notably, the catalyst tolerates functional groups of diverse electronic properties (-OMe, -Br, -Cl, -CN, -NO_2,

alkenyl, and cyclopropyl). Furthermore, it allows *N*-aryl ketimines with aryl ethyl groups (entries 17, 18) and with dialkyl substituents (entries 20-23) to be reduced with 90-97% ee's. In both metal- and organo-catalysis,[1,2,4] such substrates have rarely proved to be viable. MacMillan,[4d] List[4c] and coworkers recently reported ee's of 81-94% for dialkyl-substituted *N*-aryl ketimines in organocatalytic reduction; but for related aryl alkyl ketimines with high enantioselectivities, the alkyl group appears to be restricted to a methyl.[4d] Much lower enantioselectivities were reported for the dialkyl ketimines with homogeneous metal catalysts; in fact, none seems to give ee's higher than 80%.[12,13] Moving to *N*-alky imines, however, both the catalyst **4a** and **4b** showed very low activities in the presence of 1% **5e**, or under more acidic conditions by introduction of 3%-10% of **5e** at 20 °C (entries 24-26). A higher temperature did not help either. We speculate that a possible reason for the lost activities is the strong basicity of *N*-alkyl imines, which can coordinate to the metal of active catalyst, rendering the catalyst inactive. The hydrogenation of *N*-alkyl imines is being studied by another Ph.D student in the Xiao group.

2.2 Chiral Diamine-ligated Ir(III) and Achiral Anion System

Although the combination of chiral diamine-ligated Ir(III) and chiral phosphoric acid has demonstrated excellent enantioselectivity and good activity for a range of acyclic imines, a combination containing one chiral and one achiral entity would be even cheaper and simpler to use for catalytic hydrogenation. To realize the idea, the combination of the chiral diamine-ligated Ir(III) (*S*,*S*)-**3a** with a range of achiral acids

have been investigated for enantioselective hydrogenation of **1a**. The screening results are seen in Table 3-3.

Table 3-3. Optimization of Conditions for the Hydrogenation of **1a**[a]

entry	catalyst	additive	conv. (%)	ee (%)
1	*cat* [b]	*none*	43	3(*S*)
2	*cat* [c]	*none*	36	26(*S*)
3	(*S*,*S*)-**3a**	$HSbF_6$ (6%)	37	26(*S*)
4	(*S*,*S*)-**3a**	$TsOH.H_2O$ (6%)	98	17(*R*)
5	(*S*,*S*)-**3a**	Benzoic acid (6%)	45	29(*S*)
6	(*S*,*S*)-**3a**	Toluic acid (6%)	49	27(*S*)
7	(*S*,*S*)-**3a**	$PhB(OH)_2$ (6%)	50	66(*S*)
8	(*S*,*S*)-**3a**	1-$NpB(OH)_2$ (6%)	25	15(*S*)
9	(*S*,*S*)-**3a**	2-Me-1-$NpB(OH)_2$ (6%)	21	12(*S*)
10	(*S*,*S*)-**3a**	2-Me-$PhB(OH)_2$ (6%)	30	38(*S*)
11	(*S*,*S*)-**3a**	2-Br-$PhB(OH)_2$ (6%)	36	39(*S*)
12	(*S*,*S*)-**3a**	2-MeO-$PhB(OH)_2$ (6%)	5	-

[a] Reaction conditions: 0.5 mmol **1a**, 1 mol% catalyst, 2 mL toluene, 20 bar H_2, 20 °C, 12 h. [b] 1 mol% [Cp*Rh(TsDPEN-H)(H_2O)][SbF_6]. [c] 1 mol% [Cp*Ir(TsDPEN-H)(H_2O)][SbF_6].

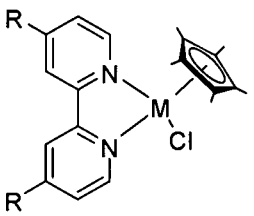
As can be seen, the ionic rhodium or iridium catalyst bearing SbF_6^- afforded 3-26% ee (entries 1-3). Furthemore, the combination of **3a** and achiral *p*-toluenesulfonic acid monohydrate afforded the amine in 98% conversion and 17% ee but with opposite configuration in comparison with other combinations (entry 4). Changing the acid to benzoic acid or toluic acid, the combination led to 29% ee (45% conversion) or 27% ee

(49% conversion) (entries 5 and 6). To our delight, the combination of **3a** and phenylboronic acid significantly improved the ee value to 66% with 50% conversion (entry 7). However, replacing the phenylboronic acid with bulky boronic acids, such as 1-NpB$(OH)_2$, 2-Me-1-NpB$(OH)_2$, 2-Me-PhB$(OH)_2$, 2-Br-PhB$(OH)_2$, or 2-MeO-PhB$(OH)_2$, all led to lower ee's and conversions (entries 8-12). The results point to that the combination of a chiral transition metal catalyst and achiral acid could afford good ee's for enantioselective hydrogenation of acyclic imines. However, more investigations will be needed in order to find catalysts of practical use.

2.3 Achiral Organometallic Complex and Chiral Anion System

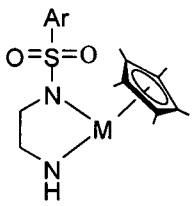
In Section 2.1 on the combination of chiral transition metal with chiral Brønsted acid, the chiral acid was considered to give a major contribution to chirality induction for enantioselective hydrogenation of acyclic imines. The design of a combination of achiral transition metal with a chiral Brønsted acid offers another potential approach to achieve good ee's for the hydrogenation. Toward this end, a range of combinations have been investigated; the results can be seen in the Table 3-4. The achiral in situ catalyst Ir-DPPP, Ir-[Ph_3P, $Ph_2P(O)H$] and **5a** afforded 10-20% conversion and 0% ee in 12 h (entries 1 and 2). Changing the Brønsted acid to the bulky **5e**, the combination of acid and Ir-DPPP or Ir-DPPE also led to 0% ee and low conversion (entries 3 and 4). Introduction of 10% iodine, the combination afforded 99% conversion in 12 h, but again no ee (entries 5 and 6). Furthermore, the combination of Pd/C and **5e** led to 99% conversion and 0% ee (entry 7). Replacing the Ir-diphosphine with ionic

Rh-diphosphine complexes, the in situ catalyst, Rh-DPPM, Rh-DPPE, Rh-DPPP, or Rh-BIPHEP and **5e**, led to 20-35% conversion and 0% ee (entries 8-11). The above results show that chiral Brønsted acid could not induce chirality in such the transitin metal-catalyzed hydrogenation, which may involve imine coordination to the metal for hydrogenation to take place. [14]



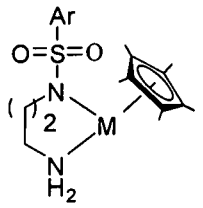
6

R = H
6a, M = Rh, **6b**, M = Ir;
R = OMe
6c, M = Rh, **6d**, M = Ir;



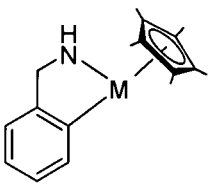
7

Ar = 4-$CH_3C_6H_4$
7a, M = Rh, **7b**, M = Ir;
Ar = 1-naphthyl
7c, M = Rh, **7d**, M = Ir;
Ar = 2,4,6-$(2\text{-}C_3H_7)_3C_6H_2$
7e, M = Rh, **7f**, M = Ir;



8

Ar = 2,4,6-$(2\text{-}C_3H_7)_3C_6H_2$
8a, M = Rh, **8b**, M = Ir;



9

9a, M = Rh, **9b**, M = Ir;

Table 3-4: Optimization of Conditions for the Hydrogenation of **1a**[a]

entry	solvent	catalyst	additive	conv. (%)	ee (%)
1[b]	DCM	Ir-DPPP[e]	**5a** (6%)	10	0
2[b]	DCM	Ir-[Ph_3P,$Ph_2P(O)H$][b]	**5a** (6%)	20	0
3[b]	DCM	Ir- DPPP[e]	**5e** (6%)	15	0
4[b]	DCM	Ir-DPPE[e]	**5e** (6%)	30	0
5[b]	DCM	Ir- DPPP[e]	**5e** (6%) + I_2	99	0
6[b]	DCM	Ir-DPPE[e]	**5e** (6%) + I_2	99	0
7[b]	DCM	Pd/C	**5e** (6%)	99	0
8[c]	DCM	Rh-DPPM[f]	**5e** (6%)	20	0
9[c]	DCM	Rh-DPPE[f]	**5e** (6%)	30	0

10[c]	DCM	Rh- DPPP[f]	**5e** (6%)	20	0
11[c]	DCM	Rh-BIPHEP[f]	**5e** (6%)	35	0
12[c]	benzene	[Cp*Rh(DPPP)]Cl[g]	**5e** (6%)+$AgSbF_6$	2	-
13[c]	benzene	[Cp*Ir(DPPP)]Cl[h]	**5e** (6%)+$AgSbF_6$	6	-
14[c]	DCM	**6a**	**5e** (6%)	0	-
15[c]	DCM	**6b**	**5e** (6%)	0	-
16[c]	DCM	**6a**	**5e** (6%)+$AgSbF_6$	1	-
17[c]	DCM	**6b**	**5e** (6%)+$AgSbF_6$	1	-
18[c]	DCM	**6c**	**5e** (6%)+$AgSbF_6$	2	0
19[c]	DCM	**6d**	**5e** (6%)+$AgSbF_6$	2	0
20[d]	toluene	**7a**	**5e** (6%)	44	0
21[d]	toluene	**7c**	**5e** (6%)	40	45(*S*)
22[d]	toluene	**7d**	**5e** (6%)	50	46(*S*)
23[d]	toluene	**7e**	**5e** (6%)	40	45(*S*)
24[d]	toluene	**7f**	**5e** (6%)	60	73(*S*)
25[d]	toluene	**8a**	**5e** (6%)	20	42(*S*)
26[d]	toluene	**9a**	**5e** (6%)	10	30(*S*)
27[d]	toluene	**9b**	**5e** (6%)	15	35(*S*)
28[d]	toluene	$[Cp^*RhCl_2]_2$	**5e** (6%)	1	-
29[d]	toluene	$[Cp^*IrCl_2]_2$	**5e** (6%)	1	-
30[d]	DCM	**7f**	**5e** (6%)	70	65(*S*)
31[d]	benzene	**7f**	**5e** (6%)	60	73(*S*)
32[d]	xylene	**7f**	**5e** (6%)	40	70(*S*)

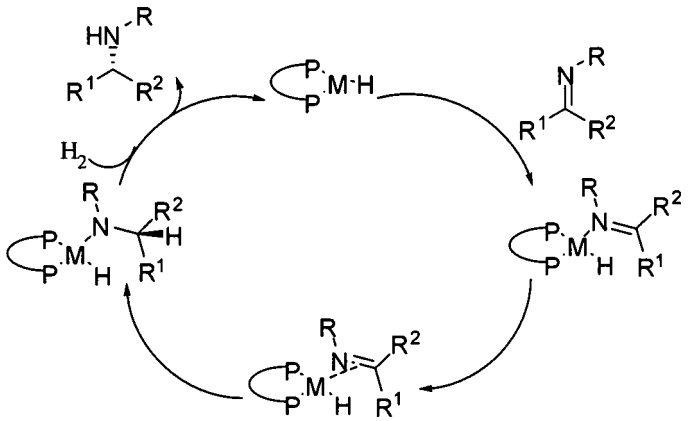
[a] Reaction conditions: 0.5 mmol **1a**, 1 mol% catalyst, 2 mL solvent, 20 °C, 12 h. [b] 40 bar H_2; [c] 30 bar H_2; [d] 20 bar H_2; [e] The in situ catalyst was prepared from $[Ir(COD)_2Cl]_2$ and phosphine in DCM. [f] The in situ catalyst prepared from $[Rh(COD)_2]BF_4$ and phosphine in DCM. [g] The in situ catalyst prepared from $[Cp^*RhCl_2]_2$ and phosphine in toluene. [h] The in situ catalyst prepared from $[Cp^*IrCl_2]_2$ and phosphine in toluene.

Following the previous direction, we searched for a catalyst which could be used for reduction via an ionic pathway. However, the combination of the in situ catalyst Cp*Rh(DPPP)Cl or Cp*Ir(DPPP)Cl and **5e** showed almost no activities for **1a** hydrogenation in the presence of 4% of $AgSbF_6$ (entries 12 and 13). Furthermore, **6a-6d** in combination with **5e** were inactive for **1a** hydrogenation, even in the presence of 4% of $AgSbF_6$ (entries 14-19). Changing to diamine-ligated catalyst, **7a** and **5e** afforded 44% conversion but no ee. Delightfully, the bulky **7c-5e**, **7d-5e** and **7e-5e** combinations led to 45% and 46% ee (entries 21-23); and the couple **7f-5e** afforded the highest ee value of 73% with 60% conversion (entry 24). However, the couples **8a-5e**, **9a-5e**, and **9b-5e** were less enantioselective (entries 25-27). Still further, $[Cp^*RhCl_2]_2$ and $[Cp^*IrCl_2]_2$ in combination with **5e** were examined, but they showed no activity for **1a** hydrogenation (entries 28 and 29). Slightly lower ee's were observed with **7f-5e** in DCM (65%), benzene (73%) and xylene (70%) (entries 30-32). Clearly, more investigations will be needed in order to find catalysts of practical use.

3 Mechanistic Aspects

For Rh and Ir diphosphine-based catalytic systems, a general catalytic cycle for imine hydrogenation has been postulated by several groups (Scheme 3-2).[14] The starting metal hydride (M-H) binds the imine via the lone pair in a η^1 manner. Following the first step, a η^1 to η^2 migration followed by insertion into the M-H bond leads to an M-amine complex. The last step is hydrogenolysis of the resulting M-N bond to generate chiral amine and the active catalyst. It needs to be pointed out that the

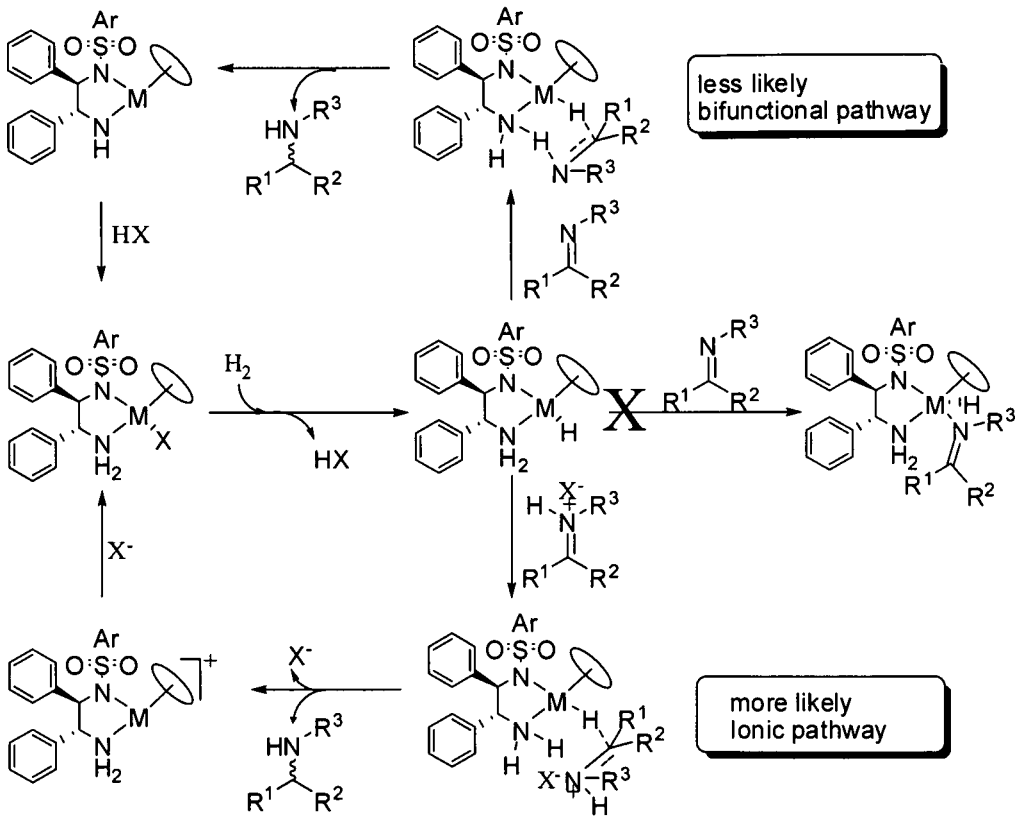
transition metal needs an empty site for imine coordination in this classical catalytic cycle.



Scheme 3-2. Classical pathway for asymmetric hydrogenation (AH) of imines with the Rh or Ir-diphosphine catalyst.

According to the our results presented above, a more likely ionic pathway is postulated for the diamine-ligated Rh/Ir catalyzed AH of imines (Scheme 3-3). Different to catalysts in the classical pathway, the metal in Cp*(N-N)M-H (M = Rh, Ir) is coordinatively saturated; the reduction could not go through a catalytic cycle in which the metal is coordinated by the imine. Furthermore, the observation in achiral Rh/Ir diphosphine and chiral Brønsted acid system suggests that chiral acids are involved in the catalytic cycle. A bifunctional pathway was proposed for asymmetric transfer hydrogenation of ketone with the similar catalyst. [15] Assuming a bifunctional pathway for the AH of imine, the reduction could take place via a six-membered pericyclic transition state involving NH hydrogen bonding with the imine rather than ion pair interaction. However, our observations suggest that the reduction is notably affected by anion on both activity and enantioselectivity, which are consistent with the

proposed ionic mechanism shown in Scheme 3-3. More detailed theoretical investigations will be carried out in the Xiao's group using NMR study and theoretical calculations.



Scheme 3-3. Proposed ionic pathway for AH of imines with Cp*Rh/Ir catalysts.

4. Conclusion

In conclusion, we have developed an efficient chiral diamine-ligated Ir(III) and chiral Bronsted acid catalytic system for asymmetric hydrogenation of the often-problematic acyclic imines. The catalyst is viable for a wide variety of imines and appears to operate via cooperative catalysis between the chiral metal catalyst and its chiral counter anion. We also explored the combination of chiral (achiral) transition metals

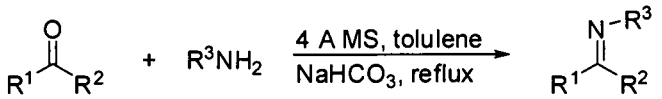
and achiral (chiral) Bronsted acids for imine hydrogenation. Preliminary investigations indicate that the simpler and cheaper catalytic systems could be realized by further exploration.

5. Experimental Section

General information

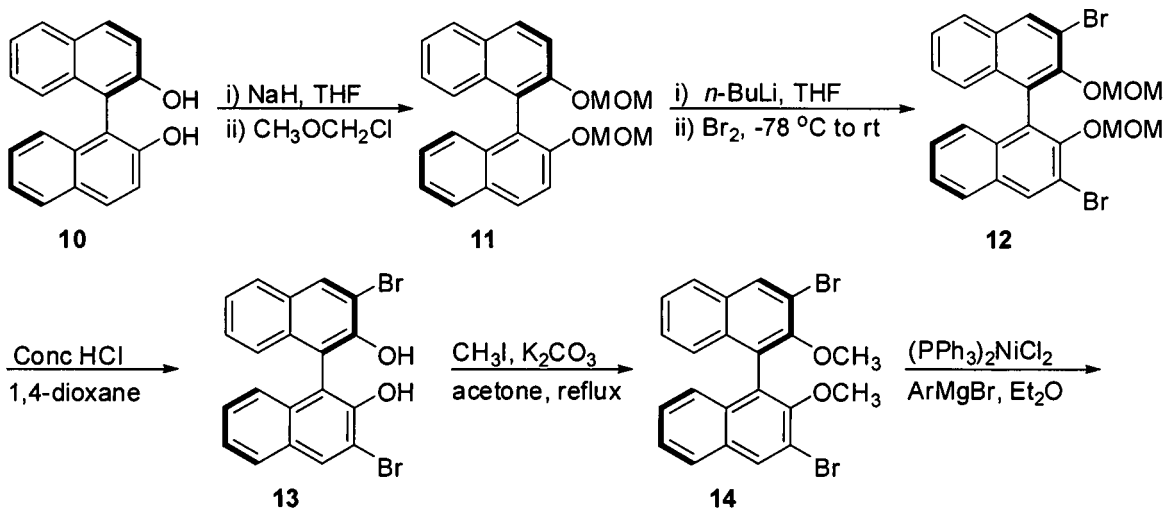
Unless otherwise specified, the chemicals were obtained commercially and used without further purification. Toluene, THF, benzene and xylene were dried over sodium and distilled prior to use. Dichloromethane (DCM) was dried over CaH_2 and distilled prior to use. Methanol was dried over Mg and distilled prior to use. ^1H NMR and ^{13}C NMR spectra were recorded on a DRX-400 spectrometer at 400 (^1H) and 100 MHz (^{13}C) in ppm with TMS as the internal standard in $CDCl_3$. The mass spectra were obtained by chemical ionization (CI). Chromatographic purification was performed on silica gel (mesh 300-400) by the flash techinique. All the products were satisfactorily characterized by ^1H and ^{13}C NMR, HRMS and elemental analysis. When possible, comparison of their NMR spectra has been made with available literature data. HPLC analysis was performed on Gilson UV/VIS-151 equipped with an OD-H or OB-H column purchased from Daicel Chemical Industries. The configuration of the products **2a**, **2b**, **2g**, **2i**, **2l**, **2m**, **2o**, **2p** and **2t** was assigned by comparison with the literature, and that of the rest was based on analogy with the assignment for other compounds without verification. The compounds **3a-c** were prepared according to the literature procedures.[15,16]

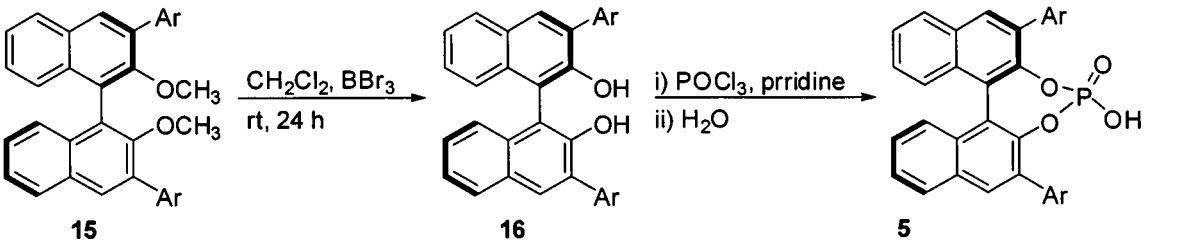
General procedure for the preparation of acyclic imines 1[17]



A 250 mL round-bottomed flask was charged with a ketone (10.0 mmol), $NaHCO_3$ (50 mmol), an amine (12.0 mmol) and activated molecular sieves (4 Å, 8 g) in anhydrous toluene (60 mL). The reaction mixture was refluxed until full conversion was reached (conversion was monitored by TLC and ^1H NMR) under nitrogen atmosphere. The reaction mixture was filtered through celite, solvent was evaporated and the crude product was was subjected to distillation or recrystallization to give pure imine. Acyclic imines **1a** to **1z** were obtained in 30% to 80% isolated yield.

Preparation of chiral phosphoric acids 5 [4d,18]





15 **16** **5**

5b: Ar = Ph;
5c: Ar = 3,5-$(CF_3)_2C_6H_3$;
5d: Ar = 1-naphthyl
5e: Ar = 2,4,6-$(2\text{-}C_3H_7)_3C_6H_2$;

Synthesis of (*R*)-2, 2'-bis(methoxymethoxy)-1,1'-binaphthyl ((*R*)-11)[18b]

To a suspension of NaH (16.0 g, 400 mmol, 60% dispersion in mineral oil, prewashed using hexane) in a mixture of dry THF (350 mL) and dry DMF (80 mL), a dry THF solution (150 mL) of (*R*)-1,1'-bi-2-naphthol (28.6 g, 100 mmol) was added dropwise under a nitrogen atmosphere at 0 °C over 30 minutes. After H_2 evolution ceased (about 2 h), chloromethyl methyl ether (30.0 g, 19.6 mL, 240 mmol) was added dropwise to the mixture, and the resulting mixture stirred overnight at room temperature. The reaction mixture was quenched with ice-water, and then THF was evaporated. The residual aqueous layer was extracted with diethyl ether (3 X 100 mL). The combined organic phase was washed twice with water, brine, and then dried over Na_2SO_4. The mixture was filtered through silica gel and dried under high vacuo for 30 min to give (*R*)-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl (35.9 g, 96%). ^{1}H NMR (400MHz, $CDCl_3$) δ (ppm): 3.14 (s, 6H), 4.97 (d, J = 6.4 Hz, 2H), 5.08 (d, J = 6.8 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 7.20-7.24 (m, 2H), 7.32-7.36 (m, 2H), 7.57 (d, J = 9.2, 2H), 7.86 (d, J = 8.0 Hz, 2H), 7.94 (d, J = 9.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 56.2, 95.6, 117.7, 121.7, 124.5, 126.0, 126.7, 128.3, 129.8, 130.3, 133.4, 153.1. MS CI

m/z (%): 392.1 $[M + NH_4]^+$; Elemental analysis calcd (%) for $C_{24}H_{22}O_4$: C, 76.99; H, 5.92; Found: C, 77.02; H, 5.92.

Synthesis of (*R*)-3, 3'-dibromo-2, 2'-bis(methoxymethoxy)-1,1'-binaphthyl ((*R*)-12)[18b]

The MOM protected (*R*)-**11** (33.7 g, 90 mmol) was dissolved in anhydrous THF (200 mL) under N_2 at -78 °C. To this solution, *n*-BuLi (84 mL, 2.5 M in hexanes, 210 mmol) was added dropwise over 30 minutes, and the solution colour changed from dark brown to yellow brown. The mixture was allowed to warm to 0 °C, and stirred for 2 h, and then cooled to –78 °C again. To the mixture was added a solution of bromine (43.2 g, 13.8 mL, 270 mmol) dropwise over 40 min and then let it warm to room temperature. After stirring over night at room temperature, the resulting mixture was poured into saturated Na_2SO_3. The organic layer was separated and aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with brine and dried over Na_2SO_4. The mixture was filtered and evaporated, the resulting crude product was purified by column chromatography on silica gel (ethyl acetate / hexane = 1 : 10) to give the product (*R*)-**12**, (38.2 g, 80%). ^{1}H NMR (400MHz, $CDCl_3$) δ (ppm): 2.55 (6H, s), 4.81 (s, 4H), 7.17 (d, J = 8.4 Hz, 2H), 7.24-7.32 (dd, J = 6.8, 8.4 Hz, 2H), 7.41 (t, J = 6.8 Hz, 2H), 7.79 (d, J = 8.0 Hz, 2H), 8.26 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 55.5, 98.3, 116.5, 125.3, 125.7, 126.5, 126.6, 127.1, 130.8, 132.2, 132.3, 149.3; ES+ for $C_{24}H_{20}{}^{79}Br_2{}^{23}NaO_4$ $[M + Na]^+$ *m/z* calcd 552.9626, found 552.9710; Elemental analysis calcd (%) for $C_{24}H_{20}Br_2O_4$: C, 54.16; H, 3.79; Found: C,

54.28; H, 3.68.

Synthesis of (*R*)-3,3'-dibromo-1,1'-bi-2-naphthol ((*R*)-13)[18b]

A mixture of (*R*)-**12** (36 g, 67.9 mmol) and concentrated HCl (4.6 mL, 150 mmol) in 1, 4-dioxane (100 mL) was heated to 50 °C and stirred overnight. The resulting mixture was poured into water (100 mL) and extracted with diethyl ether. The organic extracts were washed with brine and dried over Na_2SO_4, and evaporated in vacuo to afford 30 g crude product *R*-**13** that was used for next step without any further purification.

Synthesis of (*R*)-3,3'-dibromo-2,2'-dimethoxy-1,1'-dinaphthyl ((*R*)-14)[18c]

A suspension of crude (*R*)-**13** (30 g) was heated in acetone (300 mL) to give a homogeneous solution. To this solution were added potassium carbonate (27.6 g, 200 mmol) and methyl iodide (28.4 g, 200 mmol), and the mixture was heated at reflux for 24 h. Additional methyl iodide (3.6 g, 25 mmol) was added, and heating was continued for 4 h. The solvent was evaporated to leave a volume of 100 mL, which was cooled to room temperature and treated with 250 mL of water. The mixture was stirred for 4 h, and the resulting solid was washed with water and evaporated, and the resulting crude product was purified by column chromatography on silica gel (ethyl acetate / hexane = 1 : 10) to give the product (*R*)-**14**, (29.4 g, 92% two step yield) as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.50 (s, 6H), 7.07 (d, J = 8.4 Hz, 2H), 7.26 (t, J = 7.6 Hz, 2H), 7.41 (dd, J = 7.2, 8.0 Hz, 2H), 7.81 (d, J = 8.4 Hz, 2H), 8.26 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 61.5, 117.9, 126.2, 126.3, 127.0, 127.3, 127.6, 131.9, 133.4, 133.5, 152.9; ES+ for $C_{22}H_{16}{}^{79}Br_2{}^{23}NaO_2$ $[M + Na]^+$ *m/z* calcd 492.9415,

found 492.9396; Elemental analysis calcd (%) for $C_{22}H_{16}Br_2O_2$: C, 55.96; H, 3.42; Found: C, 55.88; H, 3.40.

Preparation of Grignard reagent[18a]

A three-neck round-bottom flask containing Mg (0.60 g, 25 mmol) was equipped with a condenser and an addition funnel. A 10.0 mL portion of a 1.0 M solution of ArBr (20 mmol in 20 mL of Et_2O) was added to the flask through the addition funnel. After 5 min, 0.10 mL (0.001 mmol) of 1,2-dibromoethane was added to the mixture. Once the solution began to reflux, the remaining ArBr solution was slowly added over 30 minutes. After the addition was complete, the reaction was allowed to reflux for 2-16 h.

Synthesis of (*R*)-15[18a]

(*R*)-3,3'-Dibromo-2,2'-dimethoxy-1,1'-dinaphthyl (2.35 g, 5 mmol) and $Ni(PPh_3)_2Cl_2$ (0.33 g, 10 mol %, 0.50 mmol) were suspended in 60 mL of Et_2O. To this suspension was added prepared Grignard reagent slowly at rt. The mixture was allowed to stir at rt for 10 min; at this point, the resulting dark green solution was refluxed for 24 h. The reaction was then allowed to cool to 0 °C and quenched slowly by the addition of 30 mL of a 1.0 M solution of HCl. The resulting aqueous layer was separated from the Et_2O layer and washed three times with excess Et_2O (30 mL). The resulting organic layers were then dried over $MgSO_4$; volatile solvents were removed in vacuo to afford the crude product as white solid that was used for next step without further purification.

Synthesis of (*R*)-16[18c]

To a solution of crude *R*-**15** (about 4.5-5.0 mmol) in 30 mL of CH_2Cl_2 was added BBr_3 (4.96 g, 20.0 mmol in 20.0 mL CH_2Cl_2) slowly at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred for 24 h. The mixture was then cooled to 0 °C, and the reaction was quenched by the slow addition of 40 mL water. Aqueous extraction with CH_2Cl_2 (3 X 40 mL), followed by drying of the organic layers over MgSO4 and removal of the solvents in vacuo, afforded an off-white solid, which was washed with hexanes, filtered, and dried in vacuo to afford crude product. Flash chromatography purification with a column of silica gel eluted with hexane/EtOAc (10/1 to 8/1) yielded the pure product in 90-95% yield (two steps).

General procedure for synthesis of (*R*)-5[4d,18c-e]

(*R*)-**16** (4 mmol) was suspended in pyridine (11.0 mL). Phosphorous oxychloride (1.2 g, 0.76 mL, 8.1 mmol) was added dropwise at room temperature with rapid stirring and the resulting suspension was heated to 80 °C. Upon reaching 80 °C all material had dissolved to provide a pale yellow clear solution The reaction mixture was stirred for 24 hours at 80 °C until all starting material was deemed consumed by TLC. The reaction mixture was cooled to 0 °C and water (10 mL) was added very slowly. The resulting biphasic suspension was heated to 80 °C for an additional 4 h. The reaction mixture was diluted with CH_2Cl_2 and the pyridine was removed via washing with 1*N* HCl. The combined organic phase was dried over Na_2SO_4, filtered and concentrated to give crude product as a pale yellow solid. Purification by flash

column chromatography (gradient from 1% to 4% MeOH in CH_2Cl_2) yielded acids **5** as a white solid.

(*R*)-3,3'-Diphenyl-1,1'-binaphyl phosphoric acid (5b)[18c]

5b was prepared from (*R*)-3,3'-diphenyl-1,1'-binaphthol. ^{1}H NMR (400MHz, $CDCl_3$) δ (ppm): 6.94-7.01 (m, 2H), 7.01-7.12 (m, 4H), 7.17-7.24 (m, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.35-7.43 (m, 2H), 7.56 (d, J = 7.6 Hz, 4H), 7.50 (brs, 1H), 7.80-7.88 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 122.6, 125.9, 126.5, 127.1, 127.7, 128.4, 128.5, 129.9, 131.4, 132.1, 134.3, 136.9, 144.8, 144.9; ^{31}P NMR ($CDCl_3$, 162 MHz) δ (ppm): 2.03; HRMS for $C_{32}H_{20}O_4P$ $[M-H]^+$: *m/z* calcd 499.1099, found 499.1085.

(*R*)-3,3'-Bis[3,5-bis(trifluoromethyl)phenyl]-1,1'-binaphthyl phosphoric acid (5c)[18d]

5c was prepared from (*R*)-3,3'-*bis*[3,5-bis(trifluoromethyl)phenyl]-1,1'-binaphthol. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.31 (d, J = 3.6 Hz, 4H), 7.47-7.51 (m, 2H), 7.76 (s, 2H), 7.95 (t, J = 4.0 Hz, 4H), 8.21 (s, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 121.3, 122.4, 123.1 (q, J_{C-F} =272.8 Hz), 126.4, 127.4, 127.6, 128.9, 130.3, 130.6, 131.2 (d, J_{P-C} = 3.2 Hz), 131.4, 131.5 (q, J_{C-F} =33.2 Hz), 133.2, 140.5, 145.7(d, J_{P-C} = 14.9 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz) δ (ppm): 5.86; HRMS for $C_{36}H_{16}O_4F_{12}P$ $[M-H]^+$: *m/z* calcd 771.0595, found 771.0557.

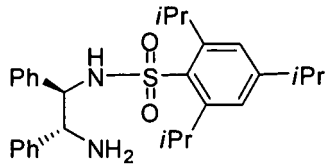
(*R*)-3,3'-*Bis*(1-naphthyl)-1,1'-binaphthyl phosphoric acid (5d)

5d was prepared from (*R*)-3,3'-bis(1-naphthyl)-1,1'- binaphthol. ^{1}H NMR (400MHz, $CDCl_3$) δ (ppm): 6.76-7.32 (m, 12H), 7.43-7.72 (m, 10H), 7.91 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 123.0, 124.9, 125.8, 126.3, 126.5, 126.8, 127.6, 127.8, 128.5, 128.6, 129.4, 131.0, 131.4, 132.5, 133.0, 133.1, 133.5, 135.7, 147.1, 147.2; ^{31}P NMR ($CDCl_3$, 162 MHz) δ (ppm): 3.08; HRMS for $C_{40}H_{24}O_4P$ $[M-H]^+$: *m/z* calcd 599.1412, found 599.1418.

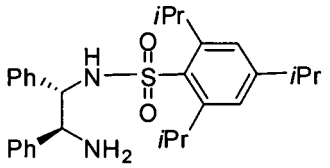
(*R*)-3,3'-Bis(2,4,6-triisopropylphenyl)-1,1'-dinaphthyl phosphoric acid (5e)[18e]

5e was prepared from3,3'-bis(2,4,6-triisopropylphenyl)-1,1'- binaphthol. ^{1}H NMR (400MHz, $CDCl_3$) δ (ppm): 0.84 (brs, 6H), 0.91(d, J = 6.8 Hz, 6H), 1.04 (d, J = 6.8 Hz, 6H), 1.09 (d, J = 6.8 Hz, 6H), 1.20 (d, J = 6.8 Hz, 12H), 2.46 (brs, 1H), 2.66 (brs, 3H), 2.80-2.87 (m, 2H), 6.97 (s, 4H), 7.22-7.27 (m, 4H), 7.39-7.43 (m, 2H), 7.77 (s, 2H), 7.83 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 23.7, 23.8, 24.4, 24.7, 25.5, 26.8, 31.2, 31.4, 34.7, 120.6, 121.5, 122.6, 122.7, 125.7, 126.4, 127.8, 128.6, 131.2, 132.7, 132.8, 132.9, 133.1, 147.1, 148.1, 148.6, 148.7; ^{31}P NMR ($CDCl_3$, 162 MHz) δ (ppm): 4.81; HRMS for $C_{50}H_{56}O_4P$ $[M-H]^+$: *m/z* calcd 751.3916, found 751.3885.

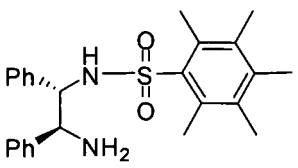
Procedure for preparation of ligand 17 to 22[19]



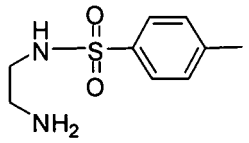
(*R*,*R*)-**17**



(*S*,*S*)-**17**



(*S*,*S*)-**18**



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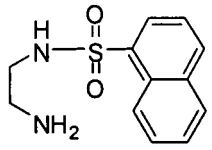

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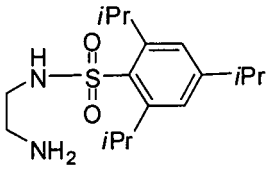

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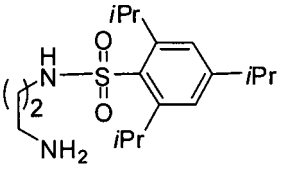


22

(1*R*, 2*R*)-(+)-1,2-Diphenylethylenediamine (424 mg, 2.0 mmol) was added in dried DCM (20 mL) and cooled down to 0 °C with an ice bath. Et_3N (0.42 mL, 3.0 mmol) was added in the solution and stirred at 0 °C for a few minutes. Then a solution of 2,4,6-triisopropylbenzenesulfonyl chloride (636 mg, 2.1 mmol) in dried DCM (15 mL) was added dropwise during 1 h period. The reaction mixture was stirred for 2 h at 0 °C, and then it was let to warm up to room temperature and stirred at room temperature overnight. The reaction mixture was washed with water (3 x 20 mL), dried over Na_2SO_4 and concentrated in vacuum to afford the crude product. Flash chromatography purification with a column of silica gel eluted with DCM/MeOH (10/1) yielded the pure product as a white solid (765 mg, 80% yield). (*S*,*S*)-**17**, (*S*,*S*)-**18**, **19**, **20**, **21**, and **22**was synthesized in a similar method.

(1*R*,2*R*)/(1*S*,2*S*)-*N*-(2,4,6-Triisopropylbenzenesulfonyl)-1,2-diphenylethylenediamine[19a]

((*R*,*R*)-**17**/(*S*,*S*)-**17**): ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.01 (d, J = 6.4 Hz, 6H),

1.08 (d, J = 6.8 Hz, 6H), 1.12 (d, J = 6.8 Hz, 6H), 1.75 (brs, 2H), 2.75 (sept, J = 6.8 Hz, 1H), 3.89 (sept, J = 6.8 Hz, 2H), 3.90 (d, J = 8.0 Hz, 1H), 4.39 (d, J = 8.0 Hz, 1H), 6.20 (brs, 1H), 6.71-6.74 (m, 2H), 6.83-6.96 (m, 7H), 7.04-7.10 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 24.0, 24.1, 25.0, 25.2, 25.3, 30.2, 30.4, 34.6, 123.7, 127.3, 127.7, 127.8, 127.9, 128.2, 128.8, 134.4, 139.1, 142.4, 150.1, 152.8; ES+ for $C_{29}H_{39}N_2O_2S$ $[M + H]^+$ *m/z* calcd 479.2732, found 479.2745; Elemental analysis calcd (%) for $C_{29}H_{38}N_2O_2S$: C, 72.76; H, 8.00; N, 5.86; Found: C, 72.84; H, 8.04; N, 5.92.

(1*S*,2*S*)-*N*-(2,3,4,5,6-Pentamethylbenzenesulfonyl)-1,2-diphenylethylenediamine ((*S*,*S*)-**18**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.81 (brs, 1H), 2.06 (s, 6H), 2.17 (s, 3H), 2.36 (s, 6H), 4.07 (d, J = 7.6 Hz, 1H), 4.36 (d, J = 7.6 Hz, 1H), 6.15 (brs, 1H), 6.86-6.89 (m, 2H), 6.96-7.07 (m, 5H), 7.08-7.14 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 17.3, 18.0, 19.2, 61.0, 64.2, 127.1, 127.5, 127.6, 127.7, 128.1, 128.6, 134.4, 134.6, 136.6, 139.1, 139.3, 142.1; ES+ for $C_{25}H_{31}N_2O_2S$ $[M + H]^+$ *m/z* calcd 423.2106, found 423.2098; Elemental analysis calcd (%) for $C_{25}H_{30}N_2O_2S$: C, 71.06; H, 7.16; N, 6.63; Found: C, 71.13; H, 7.14; N, 6.66.

***N*-(4-Methylbenzenesulfonyl)-ethylenediamine (19)**:[19a] ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 2.30 (brs, 2H), 2.43 (s, 3H), 2.79 (t, J = 5.6 Hz, 2H), 2.96 (t, J = 5.6 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 7.75 (dd, J = 1.6, 6.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 21.7, 41.3, 45.8, 127.5, 130.1, 137.5, 143.7; MS CI m/z (%): 215 $[M + H]^+$; Elemental analysis calcd (%) for $C_9H_{14}N_2O_2S$: C, 50.45; H, 6.59; N, 13.07; Found: C, 49.98; H, 6.48; N, 12.73.

***N*-(1-Naphthalenesulfonyl)-ethylenediamine (20)**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 2.71 (t, J = 5.6 Hz, 2H), 2.92 (t, J = 5.6 Hz, 2H), 2.94 (brs, 2H), 7.53 (t, J = 7.2 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.66 (t, J = 6.8 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H), 8.27 (dd, J = 1.2, 7.6 Hz, 1H), 8.67 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 41.2, 45.7, 124.6, 124.8, 127.3, 128.5, 128.8, 129.5, 130.0, 134.6, 134.7, 135.0; MS CI m/z (%): 251 $[M + H]^+$; Elemental analysis calcd (%) for $C_{12}H_{14}N_2O_2S$: C, 57.58; H, 5.64; N, 11.19; Found: C, 57.61; H, 5.64; N, 11.35.

***N*-(2,4,6-Triisopropylbenzenesulfonyl)-ethylenediamine (21)**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.25 (d, J = 6.4 Hz, 6H), 1.27 (t, J = 6.8 Hz, 12H), 2.84-2.87 (m, 2H), 2.90 (sept, J = 6.8 Hz, 1H), 2.98-3.01 (m, 2H), 4.17 (sept, J = 6.8 Hz, 2H), 7.16 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 24.0, 25.3, 30.0, 34.5, 41.2, 45.2, 124.2, 132.6, 150.7, 153.0; MS CI m/z (%): 327 $[M + H]^+$; Elemental analysis calcd (%) for $C_{17}H_{30}N_2O_2S$: C, 62.54; H, 9.26; N, 8.58; Found: C, 62.40; H, 9.22; N, 8.52.

***N*-(2,4,6-Triisopropylbenzenesulfonyl)-propylenediamine (22)**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.26 (d, J = 7.2 Hz, 6H), 1.27 (d, J = 6.8 Hz, 12H), 1.63-1.69 (m, 2H), 2.83-2.86 (m, 2H), 2.90 (sept, J = 6.8 Hz, 1H), 3.08-3.11 (m, 2H), 4.17 (sept, J = 6.8 Hz, 2H), 7.16 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 24.0, 25.3, 30.0, 31.4, 34.5, 41.5, 42.9, 124.1, 132.8, 150.5, 150.7, 152.8; MS CI m/z (%): 341.2 [M +

H]$^+$; Elemental analysis calcd (%) for $C_{18}H_{32}N_2O_2S$: C, 63.49; H, 9.47; N, 8.23; Found: C, 63.39; H, 9.48; N, 8.25.

Procedure for the preparation of complexes (*S*, *S*)-4a and (*S*, *S*)-4b

A solution of 5e (113 mg, 0.15 mmol) in DCM (5 mL) was added dropwise into a solution of (*S*, *S*)-**3a** (121 mg, 0.15 mmol) in DCM (5 mL) under a nitrogen atmosphere at room temperature over a period of 30 min. After the solution was stirred for another 30 min, the solvent was removed under reduced pressure. The resulting red solid (*S*, *S*)-**4a** (230 mg) was used for hydrogenation without further purification. (*S*, *S*)-**4b** was synthesized in a similar method. The following analytic data have been obtained.

(*S*, *S*)-**4a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.92 (d, J = 6.8 Hz, 12H), 1.11 (d, J = 6.8 Hz, 12H), 1.16 (d, J = 7.2 Hz, 12H), 1.18 (d, J = 7.2 Hz, 6H), 1.24 (d, J = 7.2 Hz, 12H), 2.02 (s, 15H), 2.54-2.62 (m, 2H), 2.68-2.79 (m, 3H), 2.85-2.91 (m, 2H), 2.94 (br, 1H), 3.73-3.80 (m, 2H), 3.93-3.95 (m, 1H), 4.02 (s, 1H), 5.36 (br, 1 H), 6.83 (s, 2H), 6.99 (s, 2H), 7.03 (s, 2H), 7.09-7.17 (m, 8H), 7.21-7.30 (m, 6H), 7.40 (t, J = 6.8 Hz, 2H), 7.77 (s, 2H), 7.85 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 10.8, 23.8, 24.1, 24.5, 24.7, 25.5, 26.9, 29.7, 31.1, 31.2, 34.4, 34.7, 73.2, 81.7, 85.7, 120.3, 121.0, 123.0, 124.9, 125.8, 126.7, 127.0, 127.3, 127.8, 128.3, 128.4, 130.7, 132.0, 133.2, 133.3, 133.4, 133.7, 134.5, 146.5, 147.4, 148.0, 148.6, 150.8, 151.0; ^{31}P NMR ($CDCl_3$, 162 MHz) δ (ppm): 7.0; MS (ES) for $[C_{39}H_{52}N_2O_2S^{193}Ir]^+$: *m/z* calcd 805.3379; found 805.3391.

(*S*, *S*)-**4b**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.94 (d, J = 6.8 Hz, 12H), 1.12 (d, J = 6.8 Hz, 6H), 1.20 (d, J = 7.2 Hz, 6H), 1.26 (d, J = 6.8 Hz, 12H), 1.99 (s, 6H), 2.00 (s, 6H), 2.06 (s, 15H), 2.16 (s, 3H), 2.58-2.64 (m, 2H), 2.70-2.79 (m, 2H), 2.86-2.93 (m, 2H), 2.99 (br, 1H), 3.95 (s, 1H), 4.00 (s, 1H), 5.17 (br, 1H), 7.00 (s, 2H), 7.04 (s, 2H), 7.13-7.31 (m, 12H), 7.40-7.44 (m, 4H), 7.99 (s, 2H), 7.86 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 9.3, 15.7, 16.4, 17.7, 22.3, 22.9, 23.2, 23.9, 25.3, 29.6, 33.1, 77.9, 78.8, 84.1, 119.2, 121.3, 123.0, 124.0, 124.8, 124.9, 125.8, 126.0, 126.1, 126.5, 128.9, 130.2, 131.4, 131.6, 131.9, 132.0, 133.9, 135.8, 143.7, 145.9, 146.1, 146.8; ^{31}P NMR ($CDCl_3$, 162 MHz) δ (ppm): 6.9; MS (ES) for $[C_{35}H_{44}N_2O_2S^{193}Ir]^+$: *m/z* calcd 749.2753; found 749.2733.

General Procedure for Preparation of Racemic Amines 2

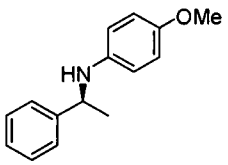
To a reaction tube charged with an acyclic imine (0.5 mmol) and $NaBH_4$ (1.0 mmol, 38 mg) were added MeOH (2 mL). The readuction was stirred at room temperature for overnight. The solution was transferred to a flask and concentrated to afford the crude product. Flash chromatography purification with a column of silica gel eluted with petroleum ether/ethyl acetate (10/1 to 8/1) yielded the desired amine product.

General procedure for asymmetric hydrogenation

To a glass liner charged with **5e** (4 mg, 5 μmol) and an imine (0.5 mmol) was added toluene (2 mL). After stirring for half minute, the catalyst **4a** (8 mg, 5 μmol) was introduced. The glass liner was then placed into an autoclave followed by degassing with H_2 three times. The hydrogenation was carried out at 20 bar H_2 with stirring at 20 °C for 15-20 h. The hydrogen gas was then carefully released, and the solution was

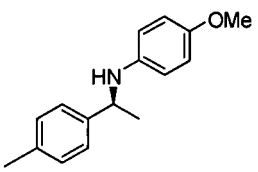
transferred to a flask and concentrated to afford the crude product. Flash chromatography purification with a column of silica gel eluted with petroleum ether/ethyl acetate (10/1 to 8/1) yielded the desired amine product.

Analytic data of products



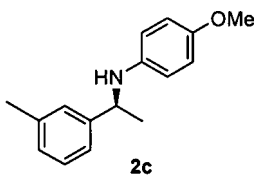
4-Methoxy-*N*-(1-phenylethyl)aniline (2a)[4c,d, 20]

2a (106 mg, 94% yield, 97% ee) was obtained according to the general procedure from the imine **1a** (113 mg, 0.5 mmol) in 15 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.48 (d, J = 6.8 Hz, 3H), 3.68 (s, 3H), 4.40 (q, J = 6.8 Hz, 1H), 6.45-6.47 (m, 2H), 6.67-6.70 (m, 2H), 7.19-7.23 (m, 1H), 7.29-7.36 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 25.6, 54.7, 56.2, 115.0, 115.2, 126.3, 127.3, 129.1, 142.0, 145.9, 152.3; HRMS for $C_{15}H_{18}NO$ $[M+H]^+$: *m/z* calcd 228.1388, found 228.1384; Elemental analysis calcd (%) for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16; Found: C, 79.19; H, 7.55; N, 6.13; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): t_R = 24.3 min (minor), t_R = 27.1 min (major).



4-Methoxy-*N*-(1-*p*-tolylethyl)aniline (2b)[4d,21]

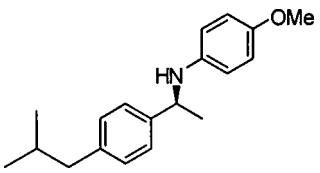
2b (112 mg, 93% yield, 97% ee) was obtained according to the general procedure from the imine **1b** (120 mg, 0.5 mmol) in 15 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.35 (d, J = 6.6 Hz, 3H), 2.20 (s, 3H), 3.58 (s, 3H), 4.27 (q, J = 6.6 Hz, 1H), 6.34-6.38 (m, 2H), 6.56-6.59 (m, 2H), 7.00 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 21.6, 25.7, 54.4, 56.2, 115.0, 115.6, 126.3, 129.8, 136.8, 142.2, 143.0, 152.3; HRMS for $C_{16}H_{20}NO$ $[M+H]^+$: *m/z* calcd 242.1545, found 242.1550; Elemental analysis calcd (%) for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80; Found: C, 79.55; H, 7.98; N, 5.75; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): t_R = 19.6 min (minor), t_R = 22.4 min (major).



2c

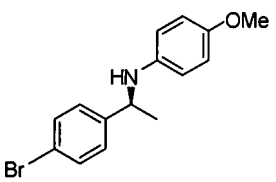
4-Methoxy-*N*-(1-*m*-tolylethyl)aniline (2c)

2c (114 mg, 95% yield, 96% ee) was obtained according to the general procedure from the imine **1c** (120 mg, 0.5 mmol) in 15 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.48 (d, J = 6.7 Hz, 3H), 2.33 (s, 3H), 3.70 (s, 3H), 4.36 (q, J = 6.7 Hz, 1H), 6.47-6.50 (m, 2H), 6.67-6.71 (m, 2H), 7.03 (d, J = 6.8 Hz, 1H), 7.14-7.25 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 21.9, 25.5, 54.8, 56.2, 115.1, 115.3, 123.4, 127.1, 128.1, 128.9, 138.6, 141.9, 145.8, 152.4; HRMS for $C_{16}H_{20}NO$ $[M+H]^+$: *m/z* calcd 242.1545, found 242.1545; Elemental analysis calcd (%) for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80; Found: C, 80.01; H, 8.02; N, 5.74; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): t_R = 21.6 min (minor), t_R = 25.3 min (major).



***N*-[1-(4-Isobutylphenyl)ethyl]-4-methoxyaniline (2d)**

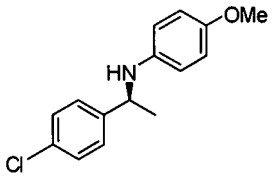
2d (133 mg, 94% yield, 98% ee) was obtained according to the general procedure from the imine **1d** (141 mg, 0.5 mmol) in 15 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.88 (d, J = 6.6 Hz, 6H), 1.47 (d, J = 6.7 Hz, 3H), 1.80-1.87 (m, 1H), 2.43 (d, J = 7.2 Hz, 2H), 3.68 (s, 3H), 4.38 (q, J = 6.7 Hz, 1H), 6.46-6.50 (m, 2H), 6.68-6.71 (m, 2H), 7.08 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 22.9, 25.4, 30.6, 45.5, 54.4, 56.2, 115.0, 115.5, 126.1, 130.0, 140.6, 142.2, 143.1, 152.3; HRMS for $C_{19}H_{26}NO$ $[M+H]^+$: *m/z* calcd 284.2014, found 284.2021; Elemental analysis calcd (%) for $C_{19}H_{25}NO$: C, 80.52; H, 8.89; N, 4.94; Found: C, 80.44; H, 9.00; N, 4.90; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): t_R = 16.7 min (minor), t_R = 19.2 min (major).



***N*-[1-(4-Bromophenyl)ethyl]-4-methoxyaniline (2e)[22]**

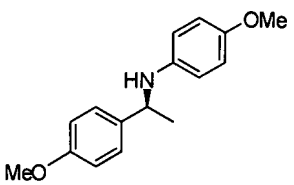
2e (141 mg, 93% yield, 97% ee) was obtained according to the general procedure from the imine **1e** (152 mg, 0.5 mmol) in 15 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.44 (d, J = 6.7 Hz, 3H), 3.67 (s, 3H), 4.34 (q, J = 6.7 Hz, 1H), 6.40-6.44 (m, 2H), 6.66-6.70 (m, 2H), 7.21-7.23 (m, 2H), 7.39-7.43 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 25.5, 54.3, 56.2, 115.0, 115.3, 120.9, 128.2, 132.1, 141.6, 145.1, 152.5;

HRMS for $C_{15}H_{17}BrNO$ $[M+H]^+$: *m/z* calcd 306.0494, found 306.0482; Elemental analysis calcd (%) for $C_{15}H_{16}BrNO$: C, 58.84; H, 5.27; N, 4.57; Found: C, 58.90; H, 5.30; N, 4.55; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 1 mL/min, λ = 254 nm): t_R = 16.0 min (minor), t_R = 19.9 min (major).



***N*-[1-(4-Chlorophenyl)ethyl]-4-methoxyaniline (2f)**[4d,21,23]

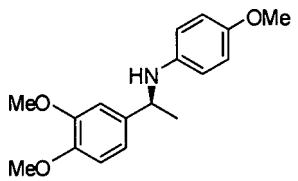
2f (122 mg, 94% yield, 96% ee) was obtained according to the general procedure from the imine **1f** (130 mg, 0.5 mmol) in 15 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.45 (d, *J* = 6.7 Hz, 3H), 3.68 (s, 3H), 4.36 (q, *J* = 6.7 Hz, 1H), 6.41-6.45 (m, 2H), 6.67-6.69 (m, 2H), 7.22-7.30 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 25.6, 54.2, 56.2, 115.1, 115.2, 127.8, 129.2, 132.8, 141.6, 144.5, 152.5; HRMS for $C_{15}H_{17}ClNO$ $[M+H]^+$: *m/z* calcd 262.0999, found 262.0998; Elemental analysis calcd (%) for $C_{15}H_{16}ClNO$: C, 68.83; H, 6.16; N, 5.35; Found: C, 69.30; H, 6.35; N, 5.73; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): t_R = 31.6 min (minor), t_R = 38.3 min (major).



4-Methoxy-*N*-[1-(4-methoxyphenyl)ethyl]aniline (2g)[4b,d,23,24]

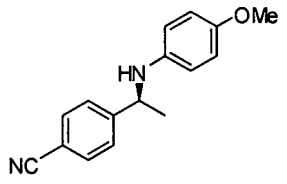
2g (119 mg, 93% yield, 97% ee) was obtained according to the general procedure from the imine **1g** (128 mg, 0.5 mmol) in 15 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.44

(d, J = 6.7 Hz, 3H), 3.65 (s, 3H), 3.73 (s, 3H), 4.34 (q, J = 6.7 Hz, 1H), 6.44-6.47 (m, 2H), 6.66-6.69 (m, 2H), 6.82-6.85 (m, 2H), 7.24-7.26 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 25.6, 54.1, 55.7, 56.2, 114.5, 115.1, 115.2, 127.4, 138.0, 142.2, 152.3, 158.9; HRMS for $C_{16}H_{20}NO_2$ $[M+H]^+$: *m/z* calcd 258.1494, found 258.1485; Elemental analysis calcd (%) for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44; Found: C, 74.74; H, 7.47; N, 5.45; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): t_R = 30.0 min (minor), t_R = 34.9 min (major).



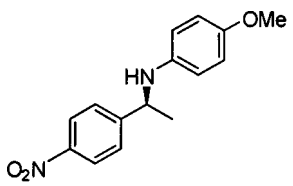
N-[1-(3,4-Dimethoxyphenyl)ethyl]-4-methoxyaniline (2h)[4c]

2h (132 mg, 92% yield, 97% ee) was obtained according to the general procedure from the imine **1h** (143 mg, 0.5 mmol) in 15 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.48 (d, J = 6.6 Hz, 3H), 3.70 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 4.34 (q, J = 6.6 Hz, 1H), 6.47-6.50 (m, 2H), 6.68-6.72 (m, 2H), 6.80-6.82 (m, 1H), 6.89-6.92 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 25.6, 54.6, 56.1, 56.2, 56.3, 109.5, 111.6, 115.0, 115.1, 118.2, 138.6, 142.1, 148.2, 149.5, 152.4; HRMS for $C_{17}H_{22}NO_3$ $[M+H]^+$: *m/z* calcd 288.1600, found 288.1606; Elemental analysis calcd (%) for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87; Found: C, 71.05; H, 7.40; N, 4.85; HPLC (Chiralcel OD-H, hexane:isopropanol:diethylamine = 90:10:0.1, flow rate 0.5 mL/min, λ = 254 nm): t_R = 25.3 min (minor), t_R = 29.0 min (major).



4-[1-(4-Methoxyphenylamino)ethyl]benzonitrile (2i)[4c]

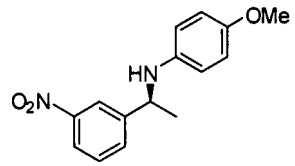
2i (118 mg, 94% yield, 93% ee) was obtained according to the general procedure from the imine **1i** (125 mg, 0.5 mmol) in 20 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.47 (d, J = 6.8 Hz, 3H), 3.67 (s, 3H), 3.86 (brs, 1H), 4.43 (q, J = 6.7 Hz, 1H), 6.38-6.41 (m, 2H), 6.67-6.70 (m, 2H), 7.45-7.48 (m, 2H), 7.56-7.58 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 25.4, 54.6, 56.1, 111.0, 114.9, 115.3, 119.5, 127.2, 133.0, 141.3, 151.9, 152.6; HRMS for $C_{16}H_{17}N_2O$ $[M+H]^+$: *m/z* calcd 253.1341, found 253.1347; Elemental analysis calcd (%) for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10; Found: C, 76.60; H, 6.60; N, 10.88; HPLC (Chiralcel OD-H, hexane:isopropanol: diethylamine = 90:10:0.1, flow rate 1 mL/min, λ = 254 nm): t_R = 18.4 min (minor), t_R = 21.8 min (major).



4-Methoxy-*N*-[1-(4-nitrophenyl)ethyl]aniline (2j)[4c,d]

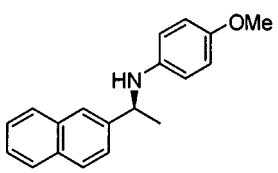
2j (126 mg, 93% yield, 92% ee) was obtained according to the general procedure from the imine **1j** (135 mg, 0.5 mmol) in 20 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.51 (d, J = 6.8 Hz, 3H), 3.68 (s, 3H), 3.87 (brs, 1H), 4.49 (q, J = 6.8 Hz, 1H), 6.39-6.42 (m, 2H), 6.67-6.70 (m, 2H), 7.52-7.54 (m, 2H), 8.15-8.17 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 25.4, 54.4, 56.1, 115.0, 115.3, 124.5, 127.2, 141.2, 147.4, 152.7, 154.0;

HRMS for $C_{15}H_{17}N_2O_3$ $[M+H]^+$: *m/z* calcd 273.1239, found 273.1236; Elemental analysis calcd (%) for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29; Found: C, 66.26; H, 5.97; N, 10.34; HPLC (Chiralcel OD-H, hexane:isopropanol: diethylamine = 90:10:0.1, flow rate 1 mL/min, λ = 254 nm): t_R = 20.4 min (minor), t_R = 22.7 min (major).



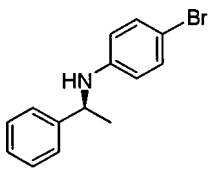
4-Methoxy-*N*-[1-(3-nitrophenyl)ethyl]aniline (2k)

2k (126 mg, 93% yield, 84% ee) was obtained according to the general procedure from the imine **1k** (135 mg, 0.5 mmol) in 20 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.52 (d, *J* = 6.8 Hz, 3H), 3.68 (s, 3H), 3.89 (brs, 1H), 4.50 (q, *J* = 6.8 Hz, 1H), 6.42-6.45 (m, 2H), 6.68-6.71 (m, 2H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 8.05-8.08 (m, 1H), 8.24 (t, *J* = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 25.5, 54.3, 56.1, 115.0, 115.3, 121.4, 122.5, 130.1, 132.7, 141.2, 148.6, 149.1, 152.7; HRMS for $C_{15}H_{17}N_2O_3$ $[M+H]^+$: *m/z* calcd 273.1239, found 273.1240; Elemental analysis calcd (%) for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29; Found: C, 65.98; H, 5.95; N, 10.24; HPLC (Chiralcel OD-H, hexane:isopropanol:diethylamine = 90:10:0.1, flow rate 1 mL/min, λ = 254 nm): t_R = 15.2 min (minor), t_R = 19.0 min (major).



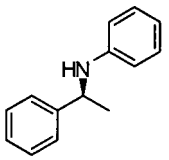
4-Methoxy-*N*-[1-(naphthalen-2-yl)ethyl]aniline (2l)[4b,c133,152]

2l (132 mg, 96% yield, 98% ee) was obtained according to the general procedure from the imine **1l** (138 mg, 0.5 mmol) in 15 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.56 (d, J = 6.7 Hz, 3H), 3.66 (s, 3H), 4.56 (q, J = 6.7 Hz, 1H), 6.49-6.53 (m, 2H), 6.65-6.69 (m, 2H), 7.40-7.50 (m, 3H), 7.77-7.81 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 25.5, 55.1, 56.1, 115.2, 115.3, 124.8, 124.9, 125.9, 126.4, 128.1, 128.3, 128.9, 133.2, 134.0, 141.8, 143.3, 152.5; HRMS for $C_{19}H_{20}NO$ $[M+H]^+$: *m/z* calcd 278.1545, found 278.1544; Elemental analysis calcd (%) for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05; Found: C, 82.23; H, 6.94; N, 4.99; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): t_R = 33.8 min (minor), t_R = 40.4 min (major).



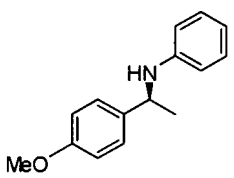
4-Bromo-*N*-(1-phenylethyl)aniline (2m)[25153]

2m (127 mg, 93% yield, 94% ee) was obtained according to the general procedure from the imine **1m** (137 mg, 0.5 mmol)in 15 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.48 (d, J = 6.8 Hz, 3H), 4.05 (brs, 1H), 4.40 (q, J = 6.8 Hz, 1H), 6.34-6.37 (m, 2H), 7.12-7.15 (m, 2H), 7.20-7.23 (m, 1H), 7.29-7.32 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 25.4, 53.9, 109.3, 115.4, 126.2, 127.5, 129.2, 132.2, 145.1, 146.6; HRMS for $C_{14}H_{15}BrN$ $[M+H]^+$: *m/z* calcd 276.0388, found 276.0389; Elemental analysis calcd (%) for $C_{14}H_{14}BrN$: C, 60.89; H, 5.11; N, 5.07; Found: C, 61.27; H, 5.27; N, 4.96; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): t_R = 25.6 min (minor), t_R = 30.4 min (major).



***N*-(1-Phenylethyl)aniline (2n)**[4b,d,20,24]

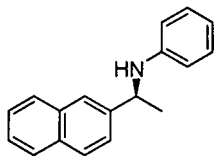
2n (92 mg, 94% yield, 95% ee) was obtained according to the general procedure from the imine **1n** (98 mg, 0.5 mmol) in 15 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.51 (d, J = 6.8 Hz, 3H), 4.02 (brs, 1H), 4.48 (q, J = 6.8 Hz, 1H), 6.49-6.52 (m, 2H), 6.62-6.66 (m, 1H), 7.06-7.11 (m, 2H), 7.20-7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 25.5, 53.9, 113.7, 117.6, 126.3, 127.3, 129.1, 129.5, 145.7, 147.7; HRMS for $C_{14}H_{16}N$ $[M+H]^+$: *m/z* calcd 198.1283, found 198.1282; Elemental analysis calcd (%) for $C_{14}H_{15}N$: C, 85.24; H, 7.66; N, 7.10; Found: C, 85.38; H, 7.71; N, 7.05; HPLC (Chiralcel OD-H, hexane:isopropanol: diethylamine = 90:10:0.1, flow rate 0.5 mL/min, λ = 254 nm): t_R = 12.7 min (major), t_R = 15.2 min (minor).



***N*-[1-(4-Methoxyphenyl)ethyl]aniline (2o)**[2c]

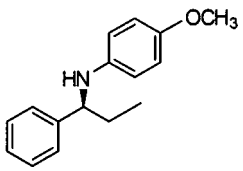
2o (105 mg, 93% yield, 97% ee) was obtained according to the general procedure from the imine **1o** (113 mg, 0.5 mmol) in 15 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.48 (d, J = 6.6 Hz, 3H), 3.77 (s, 3H), 3.98 (brs, 1H), 4.44 (q, J = 6.6 Hz, 1H), 6.49 (d, J = 8.0 Hz, 2H), 6.63 (t, J = 8.0 Hz, 1H), 6.85 (d, J = 8.0 Hz, 2H), 7.09 (t, J = 8.0 Hz, 1H), 7.27 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 25.4, 53.3, 55.7, 113.7, 114.4, 117.6, 127.3, 129.5, 137.7, 147.8, 158.9; HRMS for $C_{15}H_{18}NO$ $[M+H]^+$: *m/z* calcd 228.1388, found 228.1380; Elemental analysis calcd (%) for $C_{15}H_{17}NO$: C, 79.26;

H, 7.54; N, 6.16; Found: C, 78.90; H, 7.59; N, 5.99; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): t_R = 26.8 min (major), t_R = 30.2 min (minor).



***N*-(1-[Naphthalen-2-yl)ethyl]aniline (2p)**[4b,26,27]

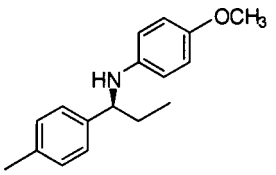
2p (116 mg, 94% yield, 95% ee) was obtained according to the general procedure from the imine **1p** (123 mg, 0.5 mmol) in 15 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.54 (d, *J* = 6.7 Hz, 3H), 4.05 (brs, 1H), 4.60 (q, *J* = 6.7 Hz, 1H), 6.52-6.66 (m, 3H), 7.04-7.08 (m, 2H), 7.38-7.48 (m, 3H), 7.75-7.79 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 25.5, 54.2, 113.9, 117.8, 124.8, 124.9, 126.0, 126.5, 128.2, 128.3, 129.0, 129.6, 133.3, 134.1, 143.3, 147.8; HRMS for $C_{18}H_{18}N$ $[M+H]^+$: *m/z* calcd 248.1439, found 248.1439; Elemental analysis calcd (%) for $C_{18}H_{17}N$: C, 87.41; H, 6.93; N, 5.66; Found: C, 87.60; H, 6.95; N, 5.58; HPLC (Chiralcel OD-H, hexane:isopropanol: diethylamine = 90:10:0.1, flow rate 0.5 mL/min, λ = 254 nm): t_R = 16.5 min (major), t_R = 18.7 min (minor).



4-Methoxy-*N*-(1-phenylpropyl)aniline (2q)[28]

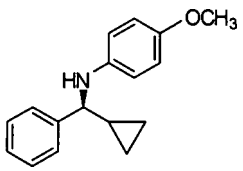
2q (110 mg, 92% yield, 90% ee) was obtained according to the general procedure from the imine **1q** (120 mg, 0.5 mmol) in 15 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.93 (t, *J* = 7.6 Hz, 3H), 1.77-1.82 (m, 2H), 3.66 (s, 3H), 4.14 (t, *J* = 6.7 Hz, 1H), 6.45-6.47 (m,

2H), 6.66-6.68 (m, 2H), 7.18-7.23 (m, 1H), 7.27-7.33 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 11.3, 32.1, 56.2, 61.0, 115.0, 115.2, 127.0, 127.3, 129.0, 142.2, 144.6, 152.3; HRMS for $C_{16}H_{20}NO$ $[M+H]^+$: *m/z* calcd 242.1545, found 242.1544; Elemental analysis calcd (%) for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80; Found: C, 79.49; H, 7.97; N, 5.78; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): t_R = 18.0 min (minor), t_R = 19.8 min (major).



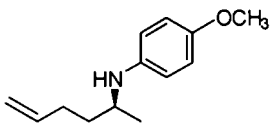
4-Methoxy-*N*-(1-*p*-tolylpropyl)aniline (2r)

2r (118 mg, 93% yield, 91% ee) was obtained according to the general procedure from the imine **1r** (127 mg, 0.5 mmol) in 15 h; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.93 (t, *J* = 7.4 Hz, 3H), 1.75-1.81 (m, 2H), 2.31 (s, 3H), 3.68 (s, 3H), 4.11 (t, *J* = 6.7 Hz, 1H), 6.45-6.48 (m, 2H), 6.66-6.69 (m, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 11.3, 21.5, 32.1, 56.2, 60.7, 114.8, 115.2, 126.9, 129.6, 136.7, 141.5, 142.3, 152.2; HRMS for $C_{17}H_{22}NO$ $[M+H]^+$: *m/z* calcd 256.1701, found 256.1702; Elemental analysis calcd (%) for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49; Found: C, 79.93; H, 8.35; N, 5.44; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): t_R = 14.8 min (minor), t_R = 16.4 min (major).



***N*-[Cyclopropyl(phenyl)methyl]-4-methoxyaniline (2s)**

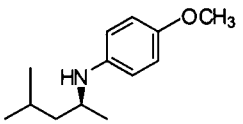
2s (116 mg, 92% yield, 97% ee) was obtained according to the general procedure from the imine **1s** (126 mg, 0.5 mmol) in 15 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.27-0.52 (m, 4H), 1.05-1.09 (m, 1H), 3.47 (d, J = 8.4 Hz, 1H), 3.57 (s, 3H), 4.02 (brs, 1H), 6.32-6.56 (m, 2H), 6.56-6.59 (m, 2H), 7.11-7.16 (m, 1H), 7.20-7.24 (m, 2H), 7.29-7.32 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 3.9, 4.7, 20.3, 56.2, 64.3, 115.1, 115.2, 127.0, 127.5, 129.0, 142.4, 144.1, 152.4; HRMS for $C_{17}H_{20}NO$ $[M+H]^+$: *m/z* calcd 254.1545, found 254.1543; Elemental analysis calcd (%) for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53; Found: C, 80.55; H, 7.60; N, 5.48; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): t_R = 19.6 min (minor), t_R = 23.7 min (major).



***N*-(Hex-5-en-2-yl)-4-methoxyaniline (2t)**[4d]

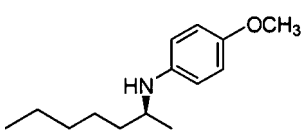
2t (90 mg, 88% yield, 95% ee) was obtained according to the general procedure from the imine **1t** (102 mg, 0.5 mmol) in 15 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.15 (d, J = 6.3 Hz, 3H), 1.45-1.54 (m, 1H), 1.61-1.70 (m, 1H), 2.13-2.19 (m, 2H), 3.10 (brs, 1H), 3.40 (q, J = 6.3 Hz, 1H), 3.74 (s, 3H), 4.95-5.05 (m, 2H), 5.79-5.86 (m, 1H), 6.54-6.57 (m, 2H), 6.76-6.78 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 21.2, 30.9, 36.7, 49.4, 56.2, 115.1, 115.2, 115.4, 138.9, 142.3, 152.3; HRMS for $C_{13}H_{20}NO$ $[M+H]^+$: *m/z* calcd 206.1545, found 206.1547; Elemental analysis calcd (%) for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82; Found: C, 76.50; H, 9.64; N, 7.02; HPLC

(Chiralcel OB-H, hexane:isopropanol = 99:1, flow rate 1.0 mL/min, λ = 254 nm): t_R = 13.4 min (major), t_R = 15.8 min (minor).



4-Methoxy-*N*-(4-methylpentan-2-yl)aniline (2u)

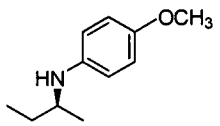
2u (93 mg, 90% yield, 92% ee) was obtained according to the general procedure from the imine **1u** (103 mg, 0.5 mmol) in 15 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.90 (d, *J* = 6.4 Hz, 3H), 0.93 (d, *J* = 6.4 Hz, 3H), 1.13 (d, *J* = 6.4 Hz, 3H), 1.19-1.26 (m, 1H), 1.42-1.49 (m, 1H), 1.73-1.77 (m, 1H), 3.09 (brs, 1H), 3.39-3.47 (m, 1H), 3.74 (s, 3H), 6.54-6.57 (m, 2H), 6.76-6.78 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 21.5, 23.0, 23.4, 25.5, 47.4, 47.9, 56.3, 115.0, 115.4, 142.4, 152.2; HRMS for $C_{13}H_{22}NO$ $[M+H]^+$: *m/z* calcd 208.1701, found 208.1706; Elemental analysis calcd (%) for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76; Found: C, 75.59; H, 10.42; N, 6.55; HPLC (Chiralcel OD-H, hexane:isopropanol = 99:1, flow rate 1.0 mL/min, λ = 254 nm): t_R = 7.0 min (minor), t_R = 7.5 min (major).



***N*-(Heptan-2-yl)-4-methoxyaniline (2v)**

2v (100 mg, 91% yield, 94% ee) was obtained according to the general procedure from the imine **1v** (110 mg, 0.5 mmol) in 15 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.89 (t, *J* = 6.8 Hz, 3H), 1.14 (d, *J* = 6.3 Hz, 3H), 1.24-1.32 (m, 4H), 1.34-1.43 (m, 3H), 1.50-1.59 (m, 1H), 3.12 (brs, 1H), 3.32-3.39 (m, 1H), 3.74 (s, 3H), 6.53-6.57 (m, 2H),

6.75-6.79 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 14.5, 21.2, 23.1, 26.3, 32.3, 37.6, 49.9, 56.2, 115.1, 115.4, 142.4, 152.2; HRMS for $C_{14}H_{24}NO$ $[M+H]^+$: *m/z* calcd 222.1858, found 222.1854; Elemental analysis calcd (%) for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33; Found: C, 76.38; H, 10.71; N, 6.28; HPLC (Chiralcel OB-H, hexane:isopropanol = 99:1, flow rate 1.0 mL/min, λ = 254 nm): t_R = 9.3 min (major), t_R = 10.6 min (minor).



***N-sec*-butyl-(4-methoxyphenyl)amine (2w)**

2w (79 mg, 88% yield, 91% ee) was obtained according to the general procedure from the imine **1w** (110 mg, 0.5 mmol) in 15 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.93(dd, 3H, *J* = 7.5, 7.5 Hz), 1.13 (d, 3H, *J* = 6.0 Hz), 1.35-1.68 (m, 2H), 3.30 (sextet, 1H, *J* = 6.4 Hz), 3.72 (s, 3H), 6.55-6.58 (m, 2H), 6.76-6.79 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 10.40, 20.27, 29.64, 50.80, 55.80, 114.70, 114.94, 141.99, 151.78; HRMS for $C_{11}H_{18}NO$ $[M+H]^+$: *m/z* calcd 180.1388, found 180.1384.; Elemental analysis calcd (%) for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81; Found: C, 73.73; H, 9.58; N, 7.84; HPLC (Chiralcel OD-H, hexane:isopropanol = 99:1, flow rate 1.0 mL/min, λ = 254 nm): t_R = 7.4 min (minor), t_R = 8.7 min (major).

6 References

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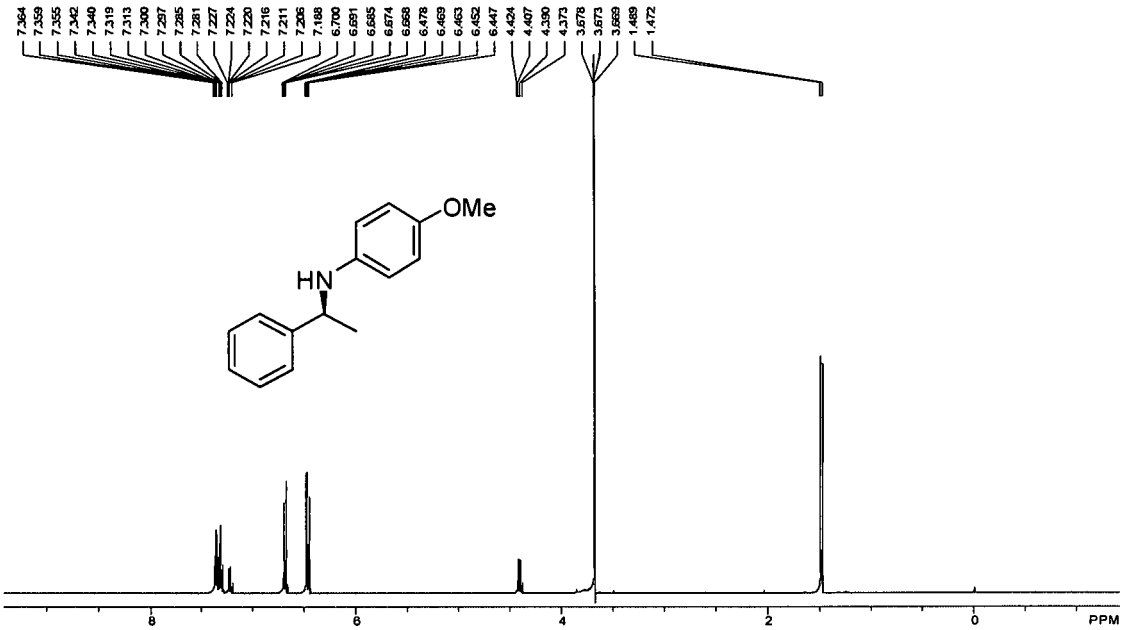
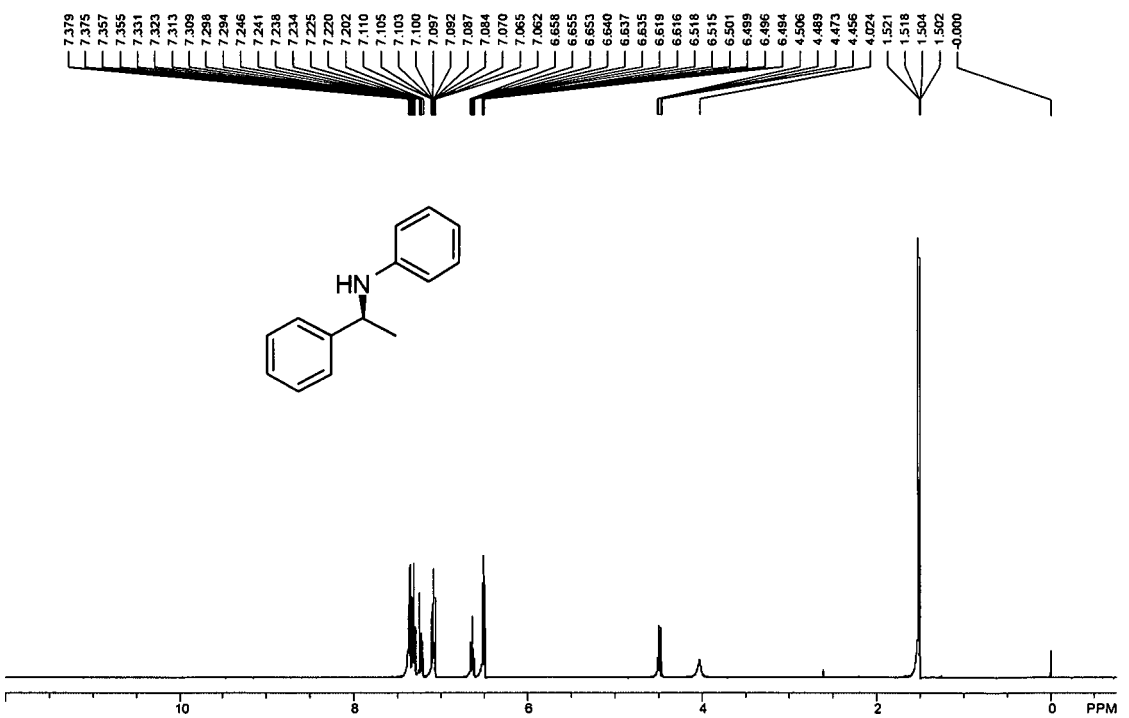
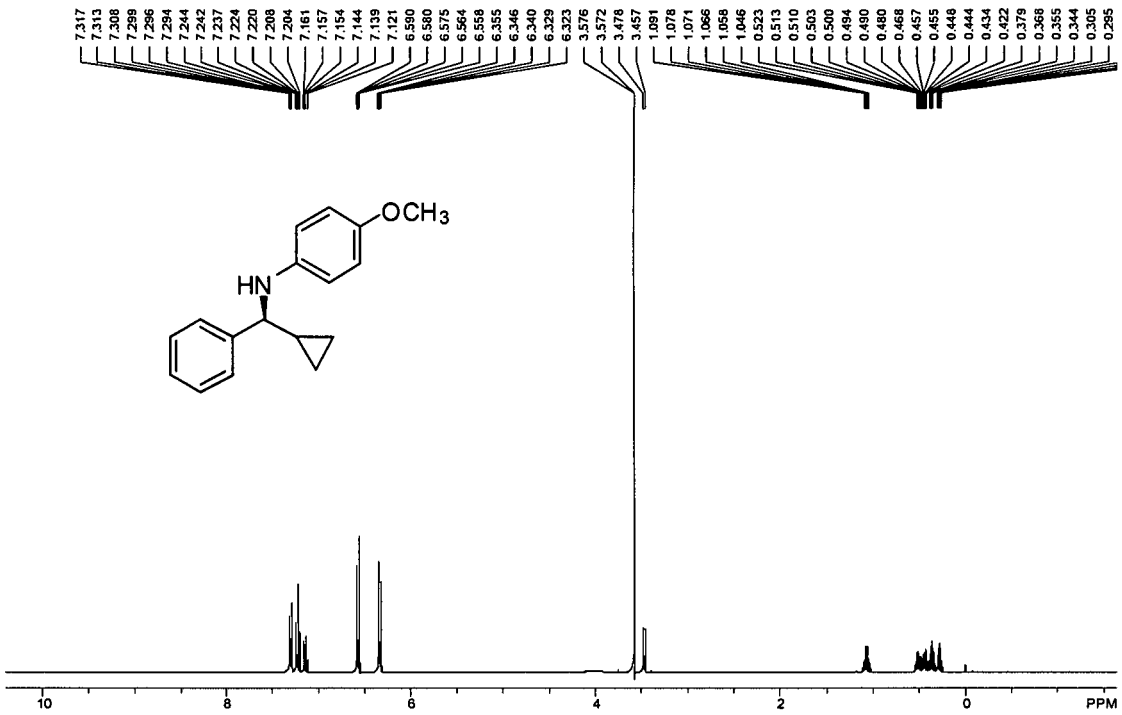
7 ^{1}H NMR Spectra (400 MHz, $CDCl_3$)



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0.510
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0.500
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6
4
2
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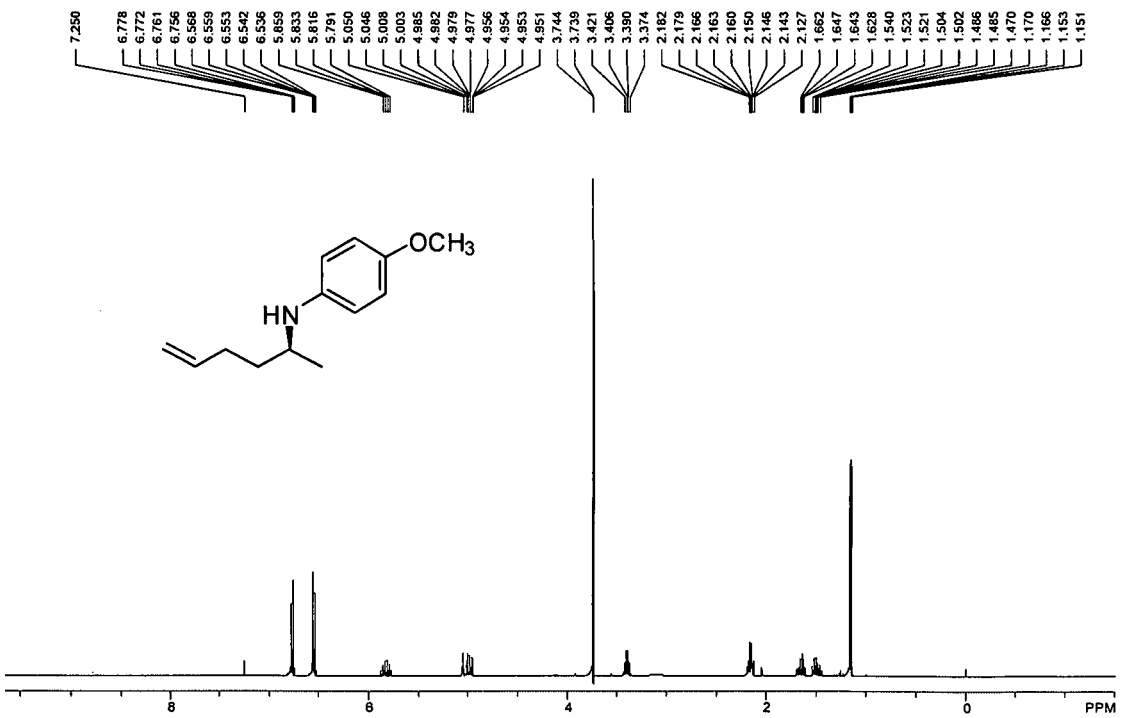
PPM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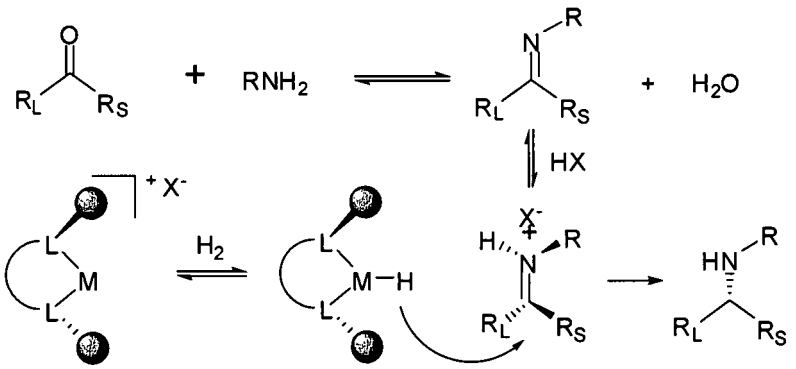
Chapter 4. Metal-Brønsted Acid Cooperative Catalysis for Asymmetric Reductive Amination

1 Introduction

Chiral amines are one of the ubiquitous functional groups in fine chemical, agrochemical and pharmaceutical products.[1] They can be accessed by asymmetric hydrogenation of imines.[1,2] A shortfall of this powerful method is the need for isolated imines as substrates, which are not always easy to synthesize due to their limited stability. The most convenient, economical, and eco-benign synthetic pathway to chiral amines is direct asymmetric reductive amination (DARA) of prochiral ketones in a one-pot fashion.[1a,3] It is surprising, however, that "few laboratory methods are known for enantioselective reductive amination"[4] and DARA remains a *key green chemistry research area*.[5] As described in Section 1.3, there are thus far only a few efficient homogeneous metal catalysts reported for DARA, displaying varying enantioselectivities for a limited range of ketones and amines.[6] A major progress has recently been made with organocatalysts by the groups of List, MacMillan and Antilla, who showed that DARA with Hantzsch esters can be catalyzed by chiral phosphoric acids, which activate the imines via protonation and induce chirality via ion pairing between the resulting phosphate anion and iminium cation.[4,7]

Inspired by the work on organocatalysis and our work in Chapter 3 on imine asymmetric hydrogenation,[8] we have carried out studies, which show that efficient DARA of ketones can be effected by cooperative catalysis of a metal catalyst and a chiral Brønsted acid, with the former reducing an in-situ generated iminium cation via

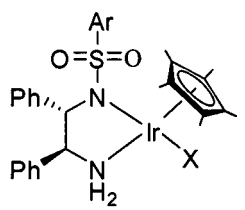
ionic hydrogenation,[9] while the latter aiding enantioselective hydride transfer via ion-pairing of its conjugate base X^- with the iminium ion (Scheme 4-1).[10] A further extension of DARA into keto esters has also been explored, but not very successful. One example of a β-amino ester was obtained in 80% ee and 99% conversion.



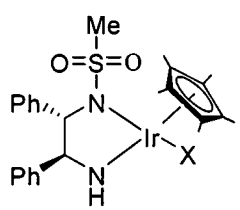
Scheme 4-1. Proposed cooperative catalysis for asymmetric reductive amination.

2 Results and Discussion

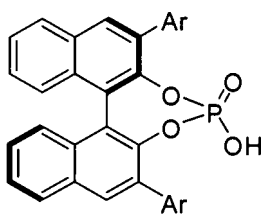
2.1 Reductive Amination of Ketones



(*S*,*S*)-**5**
Ar = 2,4,6-(2-C_3H_7)$_3C_6H_2$
a: X = Cl; **b**: X = **7**-H
c: Ar = 4-$CH_3C_6H_4$, X = **7**-H
d: Ar = 2,3,4,5,6-$(CH_3)_5C_6$, X = **7**-H



(*S*,*S*)-**6**
X = **7**-H



R-**7**
Ar = 2,4,6-(2-C_3H_7)$_3C_6H_2$

In Chapters 2 and 3, we have shown that the half-sandwich Cp*M(III)-diamine (M = Rh, Ir) catalysts enables highly enantioselective hydrogenation of cyclic and acyclic imines.[8,11] In particular, the complex **5b**, which bears a chiral phosphate

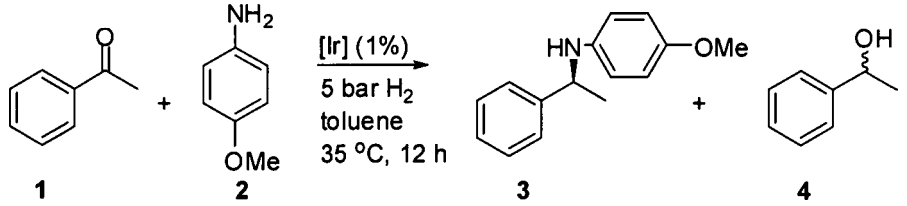
counteranion derived from the phosphoric acid *R*-**7**,[12] showed superior performance in the hydrogenation of acyclic imines, key intermediates in DARA.[8b] With these results in hand, we set out to examine the feasibility of **5** in DARA of a model ketone, acetophenone **1**, with *p*-anisidine **2** in toluene. As can be seen from Table 4-1, no reduction was observed when using **5a** or its SbF_6^- derivative at 5 bar H_2 and 35 °C (entries 1 and 2). Switching to the phosphate catalyst **5b**, a 5% conversion of **2** into the chiral amine **3** was observed (entry 3). However, under the same conditions but with no ketone present, the reduction of ketimines was much faster, affording a 94% conversion and 97% ee when using the ketimine isolated from the condensation of **1** with **2**.

Speculating that formation of the ketimine might be rate-limiting in the DARA[13] and a Brønsted acid might assist both this step and the subsequent hydrogenation[9] (Scheme 4-1), we examined the effect of **7** on the DARA. Delightfully, introduction of increasing quantities of **7** into the reaction indeed afforded a higher conversion, a higher ratio of **3**/**4** and a higher ee (entries 3-8). Thus, when 10% of **7** was added, an 81% conversion, 4/1 of **3**/**4** and an excellent ee of 97% were recorded (entry 8). Further studies revealed that the DARA went still faster in the presence of 4 Å molecular sieves (4 Å MS) (entries 2-8 vs 9-19). The combination of **5a** and 2% of $AgSbF_6$ also led to higher conversion of 5% in the presence of 4 Å MS (entry 2 vs 9). The molecular sieves are expected to facilitate the ketimine formation; however, they were less effective when added alone (entry 10). Introduction of additional amounts of **7** led to an enhanced conversion and ratio of **3**/**4** when the quantity of **7** was less than

5%; but only a slightly improved conversion was observed when the quantity of **7** was increased from 5% to 15% (entries 10-16). Thus, a 92% conversion, 10/1 of **3/4** and 97% ee were obtained when catalyst **5b**, 5% of **7** and 200 mg 4 Å MS were combined to effect the reaction. Further increase in the quantity of 4 Å MS does not appear to have any significant effect (entries 16-19). Furthermore, a lower pressure of 1 bar hydrogen led to 99/1 of **3/4** and 97% ee, but only 30% conversion (entry 20). Increasing the pressure to 10 bar or 20 bar, the reduction afforded 92% conversion (97% ee, 6/1 of **3/4**) and 90% conversion (97% ee, 5/1 of **3/4**), respectively (entries 21 and 22).

Following the optimization, the quantity of **1** also was examined for the DARA. The conversions were increased from 87% to 99% but the ratios of **3/4** were decreased form 16/1 to 3/1, when the quantities of **1** increased from 0.5 mmol to 1.5 mmol (enties 13 and 23-25). Still further, changing the reaction temperature from 35 °C to 20 °C, the reduction led to a higher enantioselectivity of 98% ee but a lower conversion of 35%. Conversely, when the temperature was set at 50 °C, the conversion was higher (95%) but the ee was lower (84%). On the other hand, the reduction afforded a near full conversion at a 5% loading of **7** in a longer time of 15 h at 35 °C (entry 28).

Table 4-1. Optimization of Conditions for the DARA of **1**[a]



entry	catalyst	P_{H2} (bar)	additive	conv. (%)[b]	**3/4**[c]	ee (%)[d]
1	**5a**	5	none	NR	-	-
2	**5a**	5	$AgSbF_6$ (2%)	NR	-	-
3	**5b**	5	None	5	1/3	-
4	**5b**	5	**7** (1%)	10	1/2	86
5	**5b**	5	**7** (3%)	44	3/1	92
6	**5b**	5	**7** (5%)	62	3/1	97
7	**5b**	5	**7** (8%)	75	3/1	97
8	**5b**	5	**7** (10%)	81	4/1	97
9	**5a**	5	4Å Ms (200 mg) + $AgSbF_6$ (2%)	5	1/1	-
10	**5b**	5	4Å Ms (200 mg)	10	1/2	90
11	**5b**	5	**7** (1%), 4Å MS (200 mg)	58	3/1	97
12	**5b**	5	**7** (3%), 4Å MS (200 mg)	82	6/1	97
13	**5b**	5	**7** (5%), 4Å MS (200 mg)	92	10/1	97
14	**5b**	5	**7** (8%), 4Å MS (200 mg)	94	10/1	97
15	**5b**	5	**7** (10%), 4Å MS (200 mg)	94	10/1	97
16	**5b**	5	**7** (15%), 4Å MS (200 mg)	94	10/1	97
17	**5b**	5	**7** (5%), 4Å MS (100 mg)	86	9/1	97
18	**5b**	5	**7** (5%), 4Å MS (400 mg)	93	10/1	97
19	**5b**	5	**7** (5%), 4Å MS (800 mg)	92	10/1	97
20	**5b**	1	**7** (5%), 4Å MS (200 mg)	30	99/1	97
21	**5b**	10	**7** (5%), 4Å MS (200 mg)	92	6/1	97
22	**5b**	20	**7** (5%), 4Å MS (200 mg)	90	5/1	97
23[e]	**5b**	5	**7** (5%), 4Å MS (200 mg)	87	16/1	97
24[f]	**5b**	5	**7** (5%), 4Å MS (200 mg)	94	5/1	97
25[g]	**5b**	5	**7** (5%), 4Å MS (200 mg)	99	3/1	97
26[h]	**5b**	5	**7** (5%), 4Å MS (200 mg)	95	5/1	84
27[i]	**5b**	5	**7** (5%), 4Å MS (200 mg)	35	6/1	98

28[j]	**5b**	5	7 (5%), 4Å MS (200 mg)	>99	10/1	97

[a] Conditions: 0.6 mmol of **1**, 0.5 mmol of **2**, 1 mol% of **5**, 2 mL of toluene, 35 °C, 12 h. [b] Conversion of **2**, determined by ^{1}H NMR analysis of crude product. [c] Molar ratio of **3/4**. [d] *S*-**3**, determined by HPLC; configuration assigned by comparison with the literature [see the experiment section]. [e] 0.5 mmol of **1**. [f] 1.0 mmol of **1**. [g] 1.5 mmol of **1**. [h] 50 °C. [i] 20 °C. [j] 15 h.

The effect of **7** on both the DARA rate and enantioselectivity is herein graphically illustrated in Figure 4-1, demonstrating that the DARA is co-catalyzed by the hydrogen-activating **5b** and the Brønsted acid **7**. The curve denoting conversion show that **7** enhance the rate of reductive amination, but its effect becomes insignificant when more than 5% is added. Note various amounts of alcohol **4** were also produced and importantly, its formation can be significantly suppressed by **7** (entries 3 and 4 vs 4-8 and 10-16).

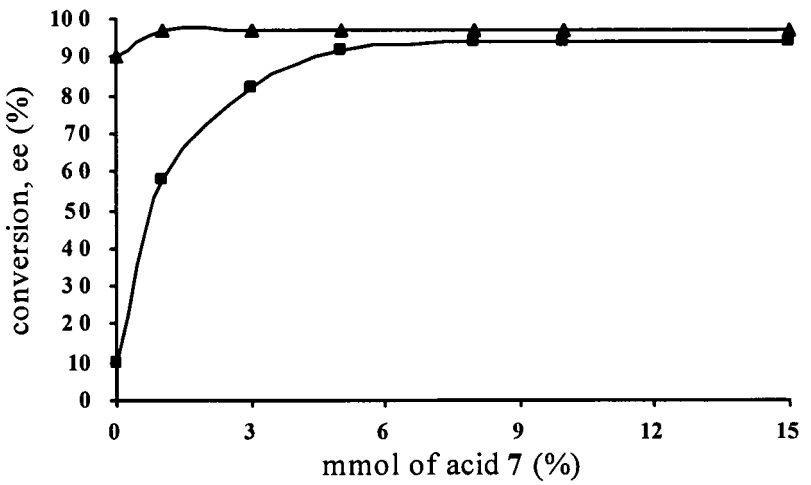
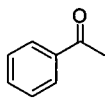
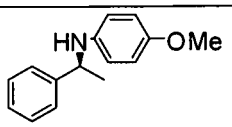
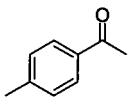
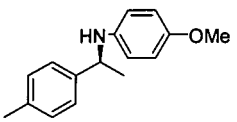
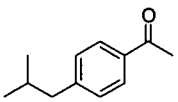
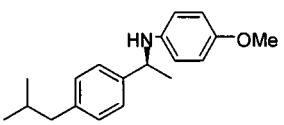
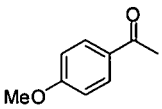
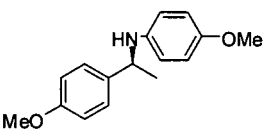
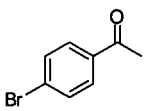
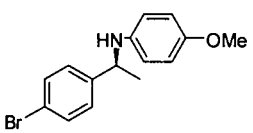
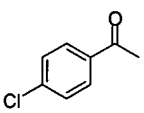
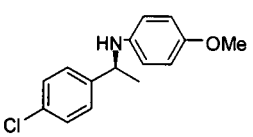
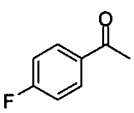
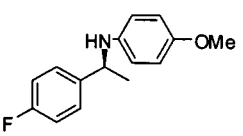
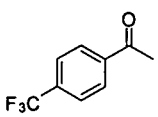
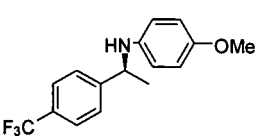
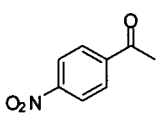
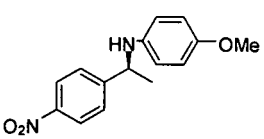
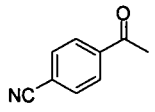
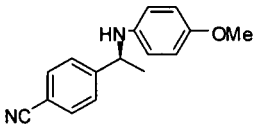
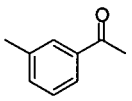
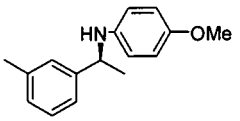
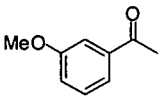
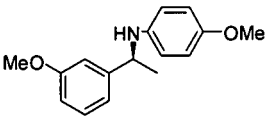
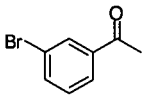
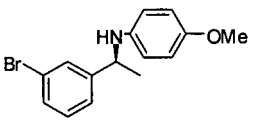
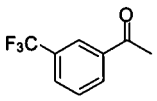
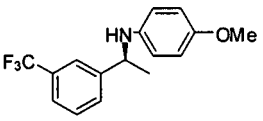
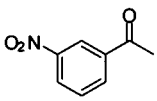
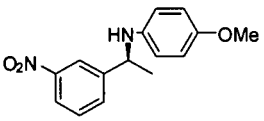
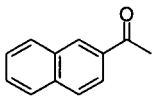
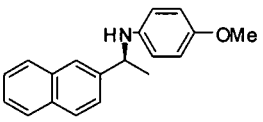
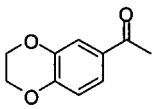
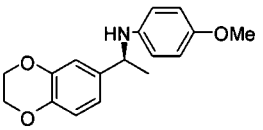
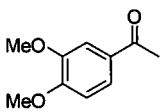
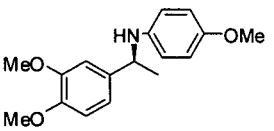


Figure 4-1. Effect of added **7** (mmol%) on the **5b**-catalyzed conversion (■) of **2** into and the enantioselectivity (▲) of **3** in the DARA of **1** in toluene in the presence of 4 Å MS at 35 °C (1 mol% of **5b**, 200 mg of MS).

Using the conditions established above, i.e. 1 mol% **5b** in the presence of 5 mol% **7** and molecular sieves, a wide range of *para* and *meta*-substituted aromatic ketones were readily aminated with **2** under 5 bar H_2 at 35 °C (Table 4-2).

Table 4-2. DARA of Aromatic Ketones with **2**[a]

entry	substrate	product	yield (%)[b]	ee (%)[c]
1			94	97
2			93	97
3			93	95
4			93	95
5			94	94
6			94	95
7			93	95
8[d]			91	91
9[d]			92	88

10[d]			92	86
11			93	94
12			93	94
13			93	94
14[d]			94	93
15[d]			88	81
16			91	96
17			92	95
18			90	93

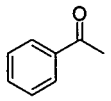
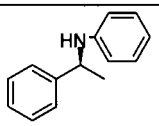
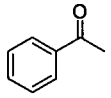
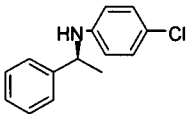
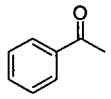
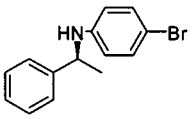
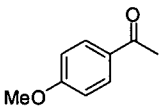
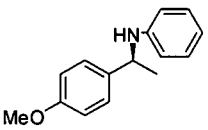
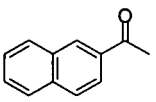
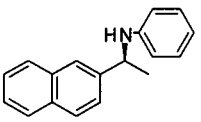
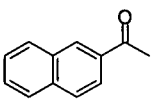
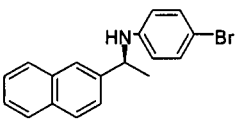
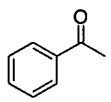
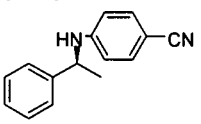
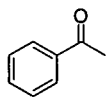
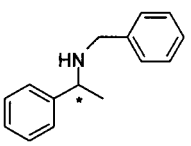
[a] Conditions: 0.6 mmol of ketone, 0.5 mmol of **2**, 1 mol% of **5b**, 5 mmol% of **7**, 2 mL of toluene, 200 mg of 4 Å MS, 5 bar of H_2, 35 °C, 15-24 h. [b] Isolated yields. [c] Determined by HPLC; configuration assigned by comparison with the literature (see the experimental section). [d] 0.7 mmol of ketone, 8 mmol% of **7**. With 5 mmol% of **7**, the ee was ca. 3% lower.

As can be seen, the amines **3** were obtained with excellent yields and ee's in almost all the cases. 4-Methoxy-*N*-(1-phenylethyl)aniline was obtained from the corresponding acetophenone in 94% yield and 97% ee (entry 1). Replacing the

acetophenone with 4'-methylacetophenone or 3'-methylacetophenone, the corresponding enantiomerically enriched amines were obtained in 97% ee (93% yield) and 94% ee (93% yield), respectively (entries 2 and 11). Changing to isobutylacetophenone, the chiral amine was also obtained in excellent ee (entry 3). Notably, the catalyst tolerates functional groups of diverse electronic properties on the ketones (-OMe, -Br, -Cl, -CN, $-NO_2$, $-CF_3$, -F); but the enantioselectivities suffered with the strongly electron-withdrawing $-NO_2$ and –CN groups (σ_p = 0.78, 0.70 respectively) (entries 9, 10 and 15). The results indicate that the enantioselectivity in DARA of para or meta- substituted ketones is more sensitive to the electron effect than steric effect. Further, enantiomerically enriched amines of 2'-acetonaphthone, 4-benzodioxan-6-yl methyl ketone, and 3',4'-dimethoxyacetophenone were also obtained in high ee's (entries 16-18). In comparison with the results of Chapter 3 on ketimine hydrogenation using **5b** at 20 °C,[8b] the DARA afforded the amines with slightly decreased enantioselectivities, but with the advantage of not isolating problematic imines.

We next investigated the DARA of aniline and its electron-deficient analogous. As shown in Table 4-3, a range of amines **3** were obtained in good yields and decent ee's. Comparing the results in Tables 4-2 (entry 1) and 4-3, it is clear that electron deficiency on the anilines reduces both the DARA yield and enantioselectivity. This is reminiscent of the observations above and, to some degree, those in organocatalysis.[4,7a] Further, the more strongly electron-withdrawing 4-aminobenzonitrile could not aminate acetophenone under the standard conditions (entry 7). In this case, we

Table 4-3. DARA with other Aniline Derivatives[a]

entry	substrate	product	yield (%)	ee (%)
1			92	93
2			86	87
3			85	85
4			92	91
5			92	91
6			75	83
7 [b]			<5	-
8 [b]			2	-

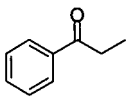
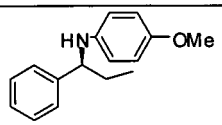
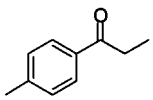
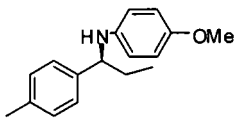
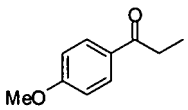
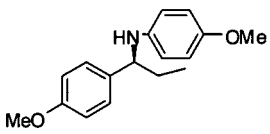
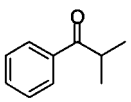
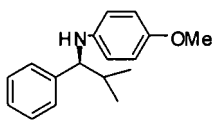
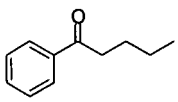
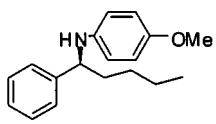
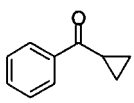
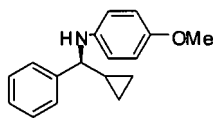
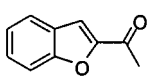
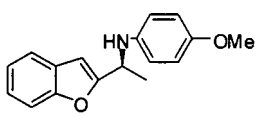
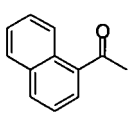
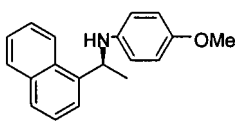
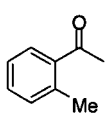
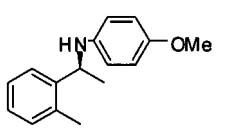
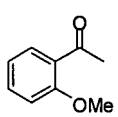
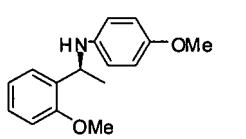
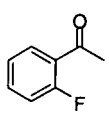
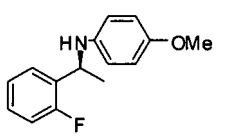
[a] Reaction conditions were the same as in Table 4-2 except with 0.7 mmol of ketones and 24 h reaction time. [b]Both (*S*,*S*)-**5b** and (*S*,*S*)-**5d** with 1-10 mol% **7** were tested for the reductive amination.

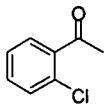
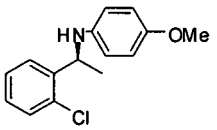
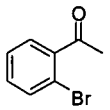
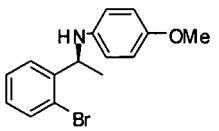
speculate that the formation of imine is a rate-limiting step because the weak nucleophile 4-aminobenzonitrile would be difficult to couple with acetophenone to form the corresponding imine, even in harsh conditions. Replacing with an electron-rich benzylamine, however, no reduction was observed either (entry 8). In

Chapter 3, we showed that catalysts **5** is inefficient for reduction of acetophenone *N*-benzylimine. This suggests that it is the reduction step that stops the DARA of ketones with benzylamine.

We encountered problems when attempting the DARA of sterically more demanding ketones. Thus, using **5b** as above, the reaction of 2'-methylacetophenone with **2** led to only a 49% ee. However, much improved enantioselectivities became accessible when less bulky metal catalysts were selected. Thus, ee's of 69%, 85% and 91% were observed with the catalysts **5d**, **5c**, and **6**, respectively. Table 4-4 summarizes the results obtained with a series of ketones. Using catalyst **5d**, α-methyl substituted chiral amines were obtained from propiophenone, 4'-methylpropiophenone and 4'-methoxypropiophenone in 91% and 92% ee's (entries 1-3). With a bulkier α position, however, isobutyrophenone showed almost no activity in this amination reaction (entry 4); *N*-[Cyclopropyl(phenyl)methyl]-4-methoxyaniline was obtained in 97% ee but only 20% yield (entry 6). Further, no reduction was observed in the DARA of 2'-bromoacetophenone (entry 13). Clearly, by replacing **5b** with the analogous **5c**, **5d** or **6** while keeping **7**, α and *ortho* substituted ketones can be aminated, affording amines in excellent enantioselectivities. We note that few metal catalysts are capable of DARA of these substrates. The results highlight one advantage of the current method, i.e. the metal and Brønsted acid catalysts can be *independently* varied to tackle a particular set of substrates.

Table 4-4. DARA of Bulkier Aromatic Ketones with **2**[a]

entry	substrate	catal	product	yield (%)	ee (%)
1		**5d**		93	92
2		**5d**		91	91
3		**5d**		91	92
4		**5d**		6	-
5		**5d**		50 35 [b] 25 [c]	75 77 [b] 76 [c]
6		**5d**		20	97
7		**5d**		93 92 [b] 92 [c] 90 [d]	91 87 [b] 87 [c] 81 [d]
8		**6**		90 91 [d] 92 [e]	87 46 [d] 69 [e]
9		**6**		92 90 [b] 92 [c] 92 [e]	91 85 [b] 49 [c] 69 [e]
10		**6**		93 92 [d]	86 49 [d]
11		**5c**		92 92 [c] 91 [d] 92 [e]	96 93 [c] 85 [d] 94 [e]

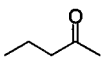
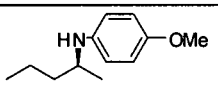
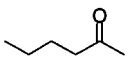
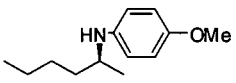
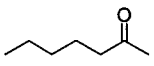
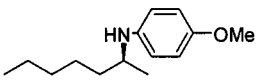
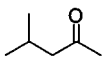
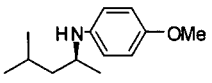
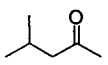
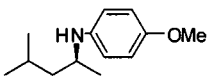
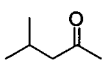
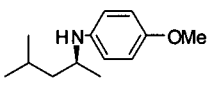
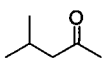
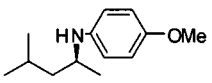
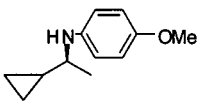
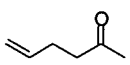
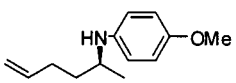
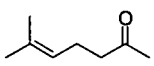
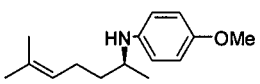
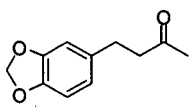
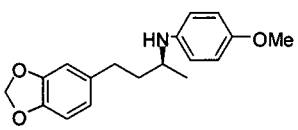
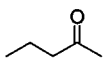
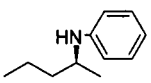
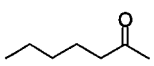
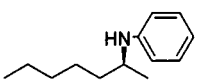
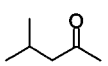
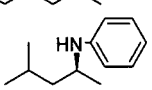
12		**6**		92 91 [d]	83 23 [d]
13		**6**		2	-

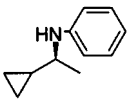
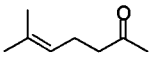
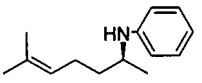
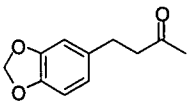
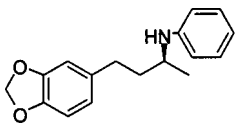
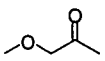
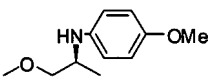
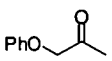
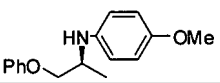
[a] Same conditions as in Table 2 except for 20-24 h. [b] **5c** as catalyst. [c] **6** as catalyst. [d] **5b** as catalyst. [e] **5d** as catalyst.

With the success in aromatic ketones, aliphatic ketones were next explored, bearing in mind in particular that there appear to be no metal catalysts capable of DARA of both aryl and aliphatic ketones. The DARA was shown to be feasible. Due to time restriction, however, the work was carried out by Barbara Villa-Marcos of the Xiao group. The results are included here simply to show the scope of the catalysis established to date. Barbara's screening established that **5d** outperformed **5b** in both enantioselectivity and conversion, and in the presence of molecular sieves, the effect of **7** on the DARA was, surprisingly somehow, less significant than in the case of aromatic ketones (Table 4-5, entries 4-7). Unlike aromatic ketones, aliphatic ketones were not reduced under the DARA conditions and so are less likely to compete with DARA. This may have partly contributed to the diminished role of **7**. However, the phosphate counteranion remains *critical*. Replacing **7**-H with SbF_6 in **5d** only led to a 42% conversion and 15% ee in the DARA shown in entry 7, Table 4-5, in 17 h. Aiming to reduce the chiral acid loading, we chose to use **5d** with no extra **7** added. As shown in Table 4-5, various aliphatic ketones were aminated with **2** and aniline, furnishing good amine yields with enantioselectivities up to 95%. Notably, the catalyst system

tolerates other reducible groups in the ketone substrates (entries 8-10, 15, 16). The easy access to these chiral amines via DARA is particularly pleasing, as the corresponding ketimines are prone to decomposition and so are difficult to isolate.

Table 4-5. DARA of Aliphatic Ketones [a]

Entry	substrate	product	yield (%)	ee (%)[b]
1			88	90
2			82	93
3			79	91
4 [c]			59 [d]	86
5 [e]			63 [d]	86
6 [f]			72 [d]	86
7			91	87
8			90	93
9			80	92
10			89	95
11			85	93
12			92	94
13			83	92
14			80	88

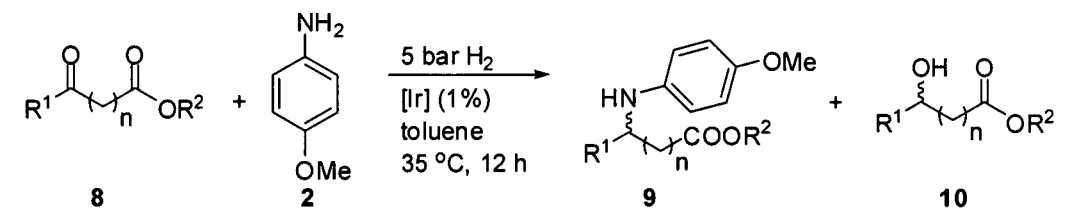
15			91	92
16			91	91
17			95	91
18			88	18
19			88	49 (55)[g]

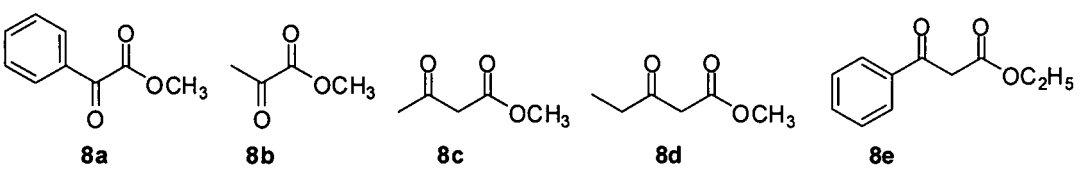
[a] Conditions: 0.55 mmol of ketone, 0.5 mmol of **2**, 1 mol% of **5d**, 2 mL of toluene, 150 mg of 4 Å MS, 5 bar of H_2, 35 °C, 12-20 h. [b] Determined by HPLC; configuration assigned by comparison with the literature (see the experimental section). [c] 5 h. [d] Conversion of **2**, determined by ^{1}H NMR analysis of the crude product. [e] 5 h, 5 mol% of **7**. [f] 5 h, 8 mol% of **7**. [g] **5b** as catalyst.

2.2 Reductive Amination of Keto Esters

To further explore the potential of the metal-Brønsted acid cooperative catalysis, DARA of α-keto esters and β-keto esters was examined. The screening results are seen in Table 4-6.

Table 4-6. DARA of Keto Esters with **2** [a]





8a **8b** **8c** **8d** **8e**

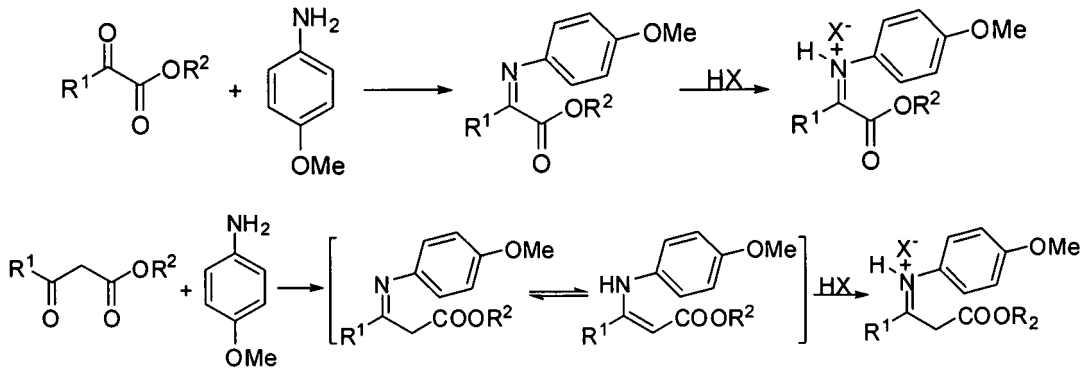
entry	substrate	catalyst	additive	conv. (%)[b]	**9/10** [c]	ee (%)[d]
1	**8a**	**5b**	none	NR	-	-
2	**8a**	**5b**	7 (1%)	NR	-	-
3	**8a**	**5b**	7 (5%)	2	1/15	-
4	**8a**	**5b**	7 (8%)	5	1/6	-
5	**8a**	**5b**	7 (10%)	5	1/6	-
6 [e]	**8a**	**5b**	7 (8%)	5	1/9	-
7 [f]	**8a**	**5b**	7 (8%)	5	1/8	-
8	**8a**	**5c**	7 (8%)	6	1/6	-
9	**8a**	**5d**	7 (8%)	6	1/6	-
10	**8a**	**6**	7 (8%)	6	1/6	-
11	**8b**	**5d**	7 (8%)	10	1/2	-
12	**8c**	**5b**	7 (8%)	70	10/1	65
13	**8c**	**5d**	7 (8%)	99	15/1	80
14	**8d**	**5b**	7 (8%)	6	1/3	-
15	**8d**	**5c**	7 (8%)	7	1/3	-
16	**8d**	**5d**	7 (8%)	9	1/2	-
17	**8d**	**6**	7 (8%)	8	1/2	-
18	**8e**	**5b**	7 (8%)	3	9/1	-
19	**8e**	**5c**	7 (8%)	5	5/1	-
20	**8e**	**5d**	7 (8%)	5	5/1	-
21	**8e**	**6**	7 (8%)	5	4/1	-
22 [e]	**8e**	**5d**	7 (8%)	5	7/1	-
23 [f]	**8e**	**5d**	7 (8%)	5	6/1	-

[a] Conditions: 0.6 mmol of **8**, 0.5 mmol of **2**, 1 mol% of **5**, 2 mL of toluene, 35 °C, 24 h. [b] Conversion of **2**, determined by ^{1}H NMR analysis of crude product. [c] Molar ratio of **9/10**. [d] Determined by HPLC analysis with a chiralpak OD-H column. [e] 50 °C. [f] 20 bar H_2.

No reduction was observed when using **5b** at 5 bar H_2 and 35 °C (entry 1). Introduction of the acid **7**, 2-5% of α-amino ester **9a** was observed and various amounts of α-imino ester and α-hydroxy ester **10a** were also produced during the reduction (entries 2-5). A higher temperature of 50 °C or a higher hydrogen pressure of 20 bar did not help either (entries 6 and 7). Changing the catalyst **5b** to **5c**, **5d** or **6**, the reduction only led to a 6% conversion and **10a** was produced as well (entries 8-10). Further, DARA of methyl pyruvate **8b** afforded 10% conversion with **9/10** = 1/2 (entry 11). To our delight, a 70% conversion (65% ee) was obtained by using the catalyst **5b** in the DARA of methyl acetoacetate **8c** (entry 12); and still better results were observed when using **5d** (entry 13). However, the catalysts **5b**, **5c**, **5d** and **6** were shown to be inefficient for the DARA of methyl 3-oxovalerate **8d** and ethyl benzoylacetate **8e**, even at a higher temperature of 50 °C or a higher hydrogen pressure of 20 bar (entries 14-23). In the DARA of **8d** and **8e**, β-amino esters (3-9%) and β-hydroxy esters were recorded; emamine esters were also observed during the reduction.

Although the catalysts **5** and acid **7** have demonstrated excellent enantioselectivity and good activity for DARA of a range of ketones, only one keto ester has been successfully aminated. In the DARA of α-keto esters, the intermediate α-imino ester has a bulky planar structure, with conjugating C=N and C=O double bonds. We speculate that the C=N bond reduction is rate-limiting for the DARA of α-keto ester because the intermediate α-imino ester was observed after the reduction. For the β-keto

ester, the reason for no reaction is probably again the reduction step, because a large amount of enamine ester was isolated after the reduction (Scheme 4-2).



Scheme 4-2. Intermediates in DARA of α-keto ester and β-keto with *p*-anisidine.

3. Conclusion

In conclusion, we have developed a new catalytic system for DARA of ketones and investigated the catalytic system for DARA of keto esters. Hinging on the cooperative catalysis of a hydrogen-activating metal cation and a Brønsted acid, this mild and operationally easy amination has been successfully demonstrated with a wide spectrum of ketones. Remarkable features of the catalytic system include: a) clean, economic H_2 as a reductant, b) wide substrate scope with high yield and enantioselectivity, and c) independent tunability of catalyst components to meet substrates of diverse properties. Further mechanistic studies and extension into other carbonyl compounds are underway in the Xiao group

4. Experimental Section

General Information

Unless otherwise specified, the chemicals were obtained commercially and used without further purification. Toluene was dried over sodium and distilled prior to use. 4 Å Molecular sieves (MS) were dried in an oven at 160 °C for a minimum of 24 h. ^{1}H NMR and ^{13}C NMR spectra were recorded on a DRX-400 spectrometer at 400 (^{1}H) and 100 MHz (^{13}C) in ppm with TMS as the internal standard in $CDCl_3$. The mass spectra were obtained by chemical ionization (CI). HPLC analysis was performed on a Gilson UV/VIS-151 equipped with an OD-H, OB-H or OJ column purchased from Daicel Chemical Industries. Chromatographic purification was performed on silica gel (mesh 300-400) by the flash techinique. All the products were satisfactorily characterized by ^{1}H and ^{13}C NMR, HRMS and elemental analysis. When possible, comparison of their NMR spectra has been made with available literature data. Compound **7** was prepared following the procedure in Chapter 3. The configuration of the products in Table 4-2 (entries 1,[6d,15-17] 4,[4,15] 8,[15] 16[4,15]) and Table 4-3 (entries 1,[15-19,4,2d] 4,[17] 5[15,17]) was assigned by comparison with the literature, and that of the rest was based on analogy with the assignment for other compounds without verification.

Procedure for the preparation of complexes (*S*,*S*)-5c and (*S*,*S*)-6

The catalysts **5a-d** and **6** were synthesized according to the procedure in the Experimental section of Chapter 3 by reacting the corresponding 16 e^- species with phosphoric acid **7**.[8a,14]

(*S*,*S*)-**5c**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.89 (d, *J* = 6.8 Hz, 12H), 1.10 (d, *J* = 6.8 Hz, 6H), 1.12 (d, *J* = 6.8 Hz, 6H), 1.16 (d, *J* = 6.8 Hz, 6H), 1.22 (d, *J* = 6.8 Hz, 6H), 1.85 (s, 15H), 2.23 (S, 3H), 2.57-2.61 (m, 3H), 2.64-2.75 (m, 1H), 2.86-2.93 (m, 1H), 2.97-3.06 (m, 1H), 4.31 (s, 1H), 4.32 (s, 1H), 5.48 (br, 1H), 6.79-7.41 (m, 29H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):10.3, 21.6, 23.7, 23.8, 24.6, 24.7, 25.5, 26.9, 31.1, 31.2, 34.7, 85.3, 86.0, 120.2, 121.0, 123.1, 124.7, 125.8, 126.7, 127.7, 128.3, 128.5, 130.7, 131.9, 133.2, 133.6, 133.9, 147.7, 147.8, 148.6; ^{31}P NMR ($CDCl_3$, 162 MHz) δ (ppm): 5.5; MS (ES) for $[C_{31}H_{36}N_2O_2S^{193}Ir]^+$: *m/z* calcd 693.2127; found 693.2115.

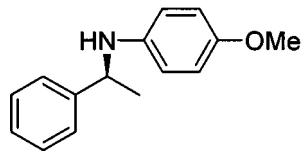
(*S*,*S*)-**6**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.91 (d, *J* = 6.4 Hz, 12H), 1.11 (d, *J* = 6.8 Hz, 6H), 1.13 (d, *J* = 6.8 Hz, 6H), 1.18 (d, *J* = 6.8 Hz, 6H), 1.24 (d, *J* = 6.8 Hz, 6H), 1.94 (s, 15H), 2.30 (s, 3H), 2.53-2.60 (m, 3H), 2.69-2.76 (m, 1H), 2.85-2.90 (m, 1H), 2.91-2.96 (m, 1H), 4.19 (s, 1H), 4.44 (s, 1H), 5.48 (br, 1H), 6.99-7.86 (m, 24H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 9.9, 10.5, 23.8, 24.5, 24.7, 25.5, 26.9, 31.1, 31.2, 34.7, 41.3 45.8, 85.6 87.8, 120.3 121.0, 123.1, 124.9, 125.8, 126.8, 126.9, 127.3, 127.8, 128.4, 128.6, 130.7, 131.9, 133.2, 133.4, 133.8, 148.0, 148.6; ^{31}P NMR ($CDCl_3$, 162 MHz) δ (ppm): 6.9; MS (ES) for $[C_{25}H_{32}N_2O_2S^{193}Ir]^+$: *m/z* calcd 617.1814; found 617.1797.

General procedure for DARA

To a glass liner equipped with a stir bar was added 4 Å MS (200 mg), **7** (19 mg, 25 mol), aromatic ketone (0.6 mmol, unless otherwise specified), amine (0.5 mmol) and toluene (2 mL). After stirring for half minute, the catalyst **5b** (5 μmol) was introduced.

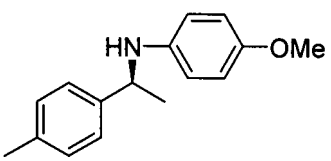
The glass liner was then placed into an autoclave, followed by degassing with H_2 three times. The hydrogenation was carried out at 5 bar H_2 with stirring at 35 °C for 15-24 h. The hydrogen gas was then carefully released in a fume hood, and the solution was filtered, transferred to a flask, and concentrated to afford the crude product. Flash chromatography purification with a column of silica gel eluted with petroleum ether/ethyl acetate (10/1 to 8/1) yielded the desired amine product.

Analytical data of products



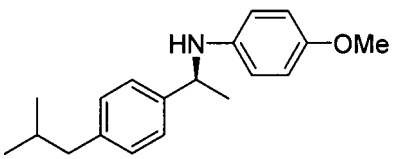
4-Methoxy-*N*-(1-phenylethyl)aniline (Table 4-2, entry 1)[2b,4,6d,7a,8a, 15-21]

The product (107 mg, 94% yield, 97% ee) was obtained according to the procedure from acetophenone (72 mg, 0.6 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 15 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49 (d, J = 6.8 Hz, 3H), 3.68 (s, 3H), 3.78 (brs, 1H), 4.41 (q, J = 6.8 Hz, 1H), 6.44-6.49 (m, 2H), 6.67-6.71 (m, 2H), 7.19-7.25 (m, 1H), 7.29-7.37 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.6, 54.7, 56.2, 115.0, 115.2, 126.3, 127.2, 129.0, 142.0, 145.9, 152.3; HRMS for $C_{15}H_{18}NO$ $[M+H]^+$: *m/z* Calcd: 228.1388; Found: 228.1395; Elemental analysis calcd (%) for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16; Found: C, 79.10; H, 7.68; N, 6.05; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): t_R = 24.7 min (minor), t_R = 28.0 min (major).



4-Methoxy-*N*-(1-*p*-tolylethyl)aniline (Table 4-2, entry 2)[2b,4,6d,7a,8a]

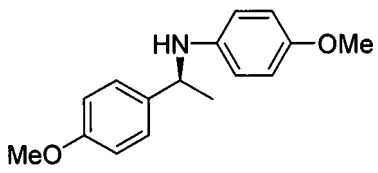
The product (112 mg, 93% yield, 97% ee) was obtained according to the procedure from 4'-methylacetophenone (80 mg, 0.6 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 15 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.48 (d, J = 6.8 Hz, 3H), 2.32 (s, 3H), 3.69 (s, 3H), 4.39 (q, J = 6.8 Hz, 1H), 6.46-6.49 (m, 2H), 6.68-6.71 (m, 2H), 7.12 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.5, 25.5, 54.4, 56.2, 115.0, 115.2, 126.2, 129.7, 136.8, 142.0, 142.9, 152.3; HRMS for $C_{16}H_{20}NO$ $[M+H]^+$: *m/z* Calcd: 242.1545; Found: 242.1544; Elemental analysis calcd (%) for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80; Found: C, 79.50; H, 7.81; N, 5.70; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 1.0 mL/min, λ = 254 nm): t_R = 11.5 min (minor), t_R = 13.5 min (major).



4-Methoxy-*N*-[1-(4-isobutylphenyl)ethyl]aniline (Table 4-2, entry 3)[8a]

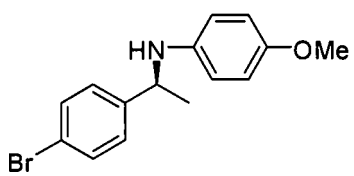
The product (132 mg, 93% yield, 95% ee) was obtained according to the procedure from 4'-isobutylacetophenone (106 mg, 0.6 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 20 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (d, J = 6.4 Hz, 6H), 1.48 (d, J = 6.8 Hz, 3H), 1.80-1.87 (m, 1H), 2.43 (d, J = 7.2 Hz, 2H), 3.69 (s, 3H), 4.39 (q, J = 6.8 Hz, 1H), 6.48-6.51 (m, 2H), 6.68-6.71 (m, 2H), 7.07 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.9, 25.3, 30.6, 45.5, 54.6, 56.2, 115.2, 126.1, 129.7, 140.7, 141.9, 142.9, 152.4; HRMS for $C_{19}H_{26}NO$ $[M+H]^+$: *m/z* Calcd: 284.2014; Found: 284.2005; Elemental analysis calcd (%) for $C_{19}H_{25}NO$: C, 80.52; H, 8.89; N,

4.94; Found: C, 80.23; H, 9.04; N, 4.84; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 1.0 mL/min, λ = 254 nm): t_R = 9.9 min (minor), t_R = 11.4 min (major).



4-Methoxy-*N*-[1-(4-methoxyphenyl)ethyl]aniline (Table 4-2, entry 4)[2b,4,6d,8a,15,16,19,20]

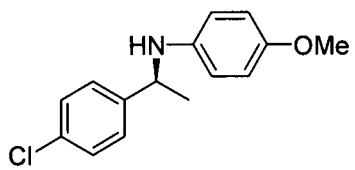
The product (120 mg, 93% yield, 95% ee) was obtained according to the procedure from 4'-methoxyacetophenone (90 mg, 0.6 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 20 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45 (d, J = 6.8 Hz, 3H), 3.68 (s, 3H), 3.76 (s, 3H), 4.36 (q, J = 6.8 Hz, 1H), 6.45-6.48 (m, 2H), 6.67-6.70 (m, 2H), 6.83-6.86 (m, 2H), 7.25-7.28 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.6, 54.1, 55.7, 56.2, 114.4, 115.1, 115.2, 127.4, 138.0, 142.1, 152.3, 158.9; HRMS for $C_{16}H_{20}NO_2$ $[M+H]^+$: *m/z* Calcd: 258.1494; Found: 258.1485; Elemental analysis calcd (%) for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44; Found: C, 74.32; H, 7.68; N, 5.32; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): t_R = 32.2 min (minor), t_R = 36.9 min (major).



***N*-[1-(4-Bromophenyl)ethyl]-4-methoxyaniline (Table 4-2, entry 5)**[8a,15]

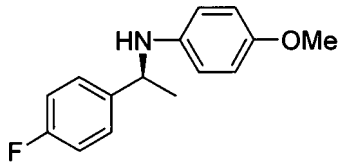
The product (143 mg, 94% yield, 94% ee) was obtained according to the procedure

from 4'-bromoacetophenone (120 mg, 0.6 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 20 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45 (d, J = 6.8 Hz, 3H), 3.69 (s, 3H), 4.35 (q, J = 6.8 Hz, 1H), 6.41-6.44 (m, 2H), 6.67-6.71 (m, 2H), 7.23-7.25 (m, 2H), 7.41-7.45 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.6, 54.2, 56.1, 115.0, 115.2, 120.8, 128.1, 132.1, 141.6, 145.1, 152.5; HRMS for $C_{15}H_{17}{}^{79}BrNO$ $[M+H]^+$: *m/z* Calcd: 306.0494; Found: 306.0488; Elemental analysis calcd (%) for $C_{15}H_{16}BrNO$: C, 58.84; H, 5.27; N, 4.57; Found: C, 58.96; H, 5.32; N, 4.43; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 1 mL/min, λ = 254 nm): t_R = 17.4 min (minor), t_R = 21.4 min (major).



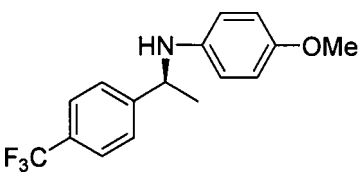
N-[1-(4-Chlorophenyl)ethyl]-4-methoxyaniline (Table 4-2, entry 6)[4,2b,6d,8a,19]

The product (123 mg, 94% yield, 95% ee) was obtained according to the procedure from 4'-chloroacetophenone (93 mg, 0.6 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 20 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.43 (d, J = 6.8 Hz, 3H), 3.66 (s, 3H), 4.35 (q, J = 6.8 Hz, 1H), 6.41-6.44 (m, 2H), 6.66-6.70 (m, 2H), 7.23-7.28 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.6, 54.2, 56.2, 115.1, 115.2, 127.8, 129.2, 132.8, 141.7, 144.6, 152.5; HRMS for $C_{15}H_{17}{}^{35}ClNO$ $[M+H]^+$: *m/z* Calcd: 262.0999; Found: 262.0993; Elemental analysis calcd (%) for $C_{15}H_{16}ClNO$: C, 68.83; H, 6.16; N, 5.35; Found: C, 69.12; H, 6.28; N, 5.14; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): t_R = 34.8 min (minor), t_R = 42.5 min (major).



_N_-[1-(4-Fluorophenyl)ethyl]-4-methoxyaniline (Table 4-2, entry 7)[4,6d,8a]

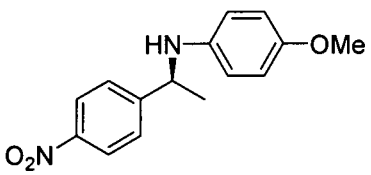
The product (114 mg, 93% yield, 95% ee) was obtained according to the procedure from 4'-fluoroacetophenone (83 mg, 0.6 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 20 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45 (d, J = 6.8 Hz, 3H), 3.68 (s, 3H), 4.38 (q, J = 6.8 Hz, 1H), 6.44 (d, J = 8.4 Hz, 2H), 6.68 (d, J = 8.4 Hz, 2H), 6.98 (t, J = 8.4 Hz, 2H), 7.31 (dd, J = 7.6, 6.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.6, 54.2, 56.1, 115.1, 115.2, 115.8 (d, J_{CF} = 21.4 Hz), 127.8 (d, J_{CF} = 8.0 Hz), 141.5 (d, J_{CF} = 2.7 Hz), 141.7, 152.5, 162.2 (d, J_{CF} = 242.7 Hz); HRMS for $C_{15}H_{17}FNO$ $[M+H]^+$: *m/z* Calcd: 246.1294; Found: 246.1295; Elemental analysis calcd (%) for $C_{15}H_{16}FNO$: C, 73.45; H, 6.57; N, 5.71; Found: C, 73.67; H, 6.68; N, 5.44; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 1.0 mL/min, λ = 254 nm): t_R = 16.5 min (minor), t_R = 20.0 min (major).



4-Methoxy-_N_-{1-[4-(trifluoromethyl)phenyl]ethyl}aniline (Table 4-2, entry 8)[15,18,20]

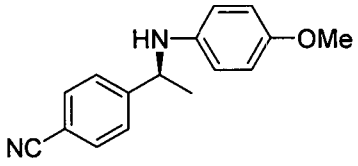
The product (134 mg, 91% yield, 91% ee) was obtained according to the procedure from 4'-trifluoroacetophenone (132 mg, 0.7 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 24 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.48 (d, J = 6.8 Hz, 3H), 3.68 (s, 3H), 3.81 (brs,

1H), 4.44 (q, J = 6.8 Hz, 1H), 6.40-6.44 (m, 2H), 6.67-6.71 (m, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.55 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.5, 54.5, 56.1, 115.0, 115.3, 124.7 (q, J_{CF} = 270.2 Hz), 126.0 (q, J_{CF} = 3.4 Hz), 126.7, 129.4 (q, J_{CF} = 32.4 Hz), 141.6, 150.3, 152.6; HRMS for $C_{16}H_{17}F_3NO$ $[M+H]^+$: *m/z* Calcd: 296.1262; Found: 296.1264; Elemental analysis calcd (%) for $C_{16}H_{16}F_3NO$: C, 65.08; H, 5.46; N, 4.74; Found: C, 65.27; H, 5.48; N, 4.49; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 1.0 mL/min, λ = 254 nm): t_R = 18.1 min (minor), t_R = 25.1 min (major).



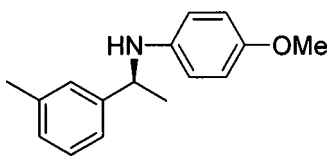
4-Methoxy-*N*-[1-(4-nitrophenyl)ethyl]aniline (Table 4-2, entry 9)[4,7a,8a]

The product (125 mg, 92% yield, 88% ee) was obtained according to the procedure from 4'-nitroacetophenone (116 mg, 0.7 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 24 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.40 (d, J = 6.4 Hz, 3H), 3.57 (s, 3H), 3.84 (brs, 1H), 4.38 (q, J = 6.8 Hz, 1H), 6.28-6.32 (m, 2H), 6.56-6.60 (m, 2H), 7.41 (d, J = 8.8 Hz, 2H), 8.04 (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.3, 54.4, 56.1, 115.0, 115.3, 124.5, 127.3, 141.2, 147.4, 152.7, 154.1; HRMS for $C_{15}H_{17}N_2O_3$ $[M+H]^+$: *m/z* Calcd: 273.1239; Found: 273.1245; Elemental analysis calcd (%) for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29; Found: C, 66.38; H, 6.02; N, 10.08; HPLC (Chiralcel OD-H, hexane:isopropanol: diethylamine = 90:10:0.1, flow rate 1 mL/min, λ = 254 nm): t_R = 29.5 min (minor), t_R = 33.1 min (major).



4-[1-(4-Methoxyphenylamino)ethyl]benzonitrile (Table 4-2, entry 10)[7a,8a]

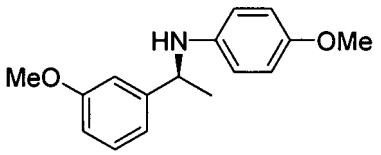
The product (116 mg, 92% yield, 86% ee) was obtained according to the procedure from 4-acetylbenzonitrile (102 mg, 0.7 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 24 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47 (d, J = 6.8 Hz, 3H), 3.67 (s, 3H), 3.86 (brs, 1H), 4.43 (q, J = 6.8 Hz, 1H), 6.38-6.41 (m, 2H), 6.67-6.70 (m, 2H), 7.45-7.48 (m, 2H), 7.56-7.58 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.4, 54.6, 56.1, 111.0, 114.9, 115.2, 119.5, 127.2, 133.0, 141.3, 151.9, 152.6; HRMS for $C_{16}H_{17}N_2O$ $[M+H]^+$: *m/z* Calcd: 253.1341; Found: 253.1349; Elemental analysis calcd (%) for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10; Found: C, 76.44; H, 6.45; N, 10.92; HPLC (Chiralcel OD-H, hexane:isopropanol: diethylamine = 90:10:0.1, flow rate 1 mL/min, λ = 254 nm): t_R = 28.9 min (minor), t_R = 34.5 min (major).



4-Methoxy-*N*-(1-*m*-tolylethyl)aniline (Table 4-2, entry 11)[2b,6d,8a]

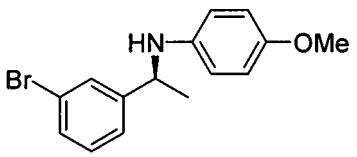
The product (112 mg, 93% yield, 94% ee) was obtained according to the procedure from 3'-methylacetophenone (80 mg, 0.6 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 20 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47 (d, J = 6.8 Hz, 3H), 2.32 (s, 3H), 3.68 (s, 3H), 4.36 (q, J = 6.8 Hz, 1H), 6.47 (d, J = 8.8 Hz, 2H), 6.69 (d, J = 8.8 Hz, 2H), 7.03 (d, J = 7.2 Hz, 1H), 7.14-7.22 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.0, 25.6, 54.7, 56.2, 115.0, 115.2, 123.3, 127.0, 128.1, 128.9, 138.6, 142.1, 146.0, 152.3; HRMS

for $C_{16}H_{20}NO$ $[M+H]^+$: *m/z* Calcd: 242.1545; Found: 242.1544; Elemental analysis calcd (%) for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80; Found: C, 79.88; H, 8.11; N, 5.68; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): t_R = 21.1 min (minor), t_R = 24.7 min (major).



4-Methoxy-*N*-[1-(3-methoxyphenyl)ethyl]aniline (Table 4-2, entry 12)[2b]

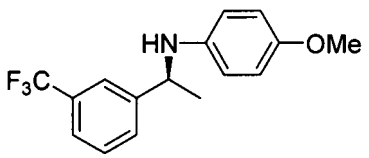
The product (120 mg, 93% yield, 94% ee) was obtained according to the procedure from 3'-methoxyacetophenone (90 mg, 0.6 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 20 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47 (d, *J* = 6.8 Hz, 3H), 3.66 (s, 3H), 3.75 (s, 3H), 3.93 (brs, 1H), 4.36 (q, *J* = 6.8 Hz, 1H), 6.46-6.49 (m, 2H), 6.65-6.69 (m, 2H), 6.74 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.93-6.95 (m, 2H), 7.21 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.4, 55.0, 55.6, 56.1, 112.2, 112.5, 115.1, 115.2 118.8, 130.1, 141.7, 147.7, 152.5, 160.4; HRMS for $C_{16}H_{20}NO_2$ $[M+H]^+$: *m/z* Calcd: 258.1494; Found: 258.1487; Elemental analysis calcd (%) for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44; Found: C, 74.52; H, 7.58; N, 5.33; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): t_R = 34.7 min (minor), t_R = 40.5 min (major).



***N*-[1-(3-bromophenyl)ethyl]-4-methoxyaniline (Table 4-2, entry 13)**[20]

The product (142 mg, 93% yield, 94% ee) was obtained according to the procedure

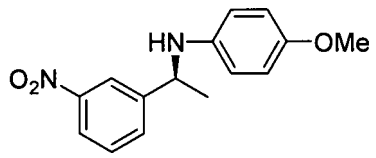
from 3'-bromoacetophenone (119 mg, 0.6 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 20 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.46 (d, J = 6.8 Hz, 3H), 3.69 (s, 3H), 4.35 (q, J = 6.8 Hz, 1H), 6.42-6.46 (m, 2H), 6.68-6.71 (m, 2H), 7.16 (t, J = 8.0 Hz, 1H), 7.28 (d, J = 8.0, 1H), 7.34 (d, J = 8.0, 1H), 7.51 (t, J = 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.6, 54.4, 56.2, 115.0, 115.2, 123.2, 125.0, 129.5, 130.4, 130.7, 141.6, 148.6, 152.5; HRMS for $C_{15}H_{17}{}^{79}BrNO$ $[M+H]^+$: *m/z* Calcd: 306.0494; Found: 306.0491; Elemental analysis calcd (%) for $C_{15}H_{16}BrNO$: C, 58.84; H, 5.27; N, 4.57; Found: C, 58.96; H, 5.33; N, 4.44; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): t_R = 18.6 min (minor), t_R = 22.6 min (major).



4-Methoxy-*N*-{1-[3-(trifluoromethyl)phenyl]ethyl}aniline (Table 4-2, entry 14)

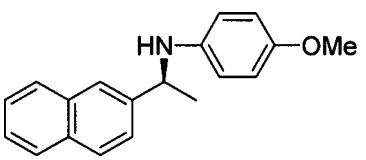
The product (139 mg, 94% yield, 93% ee) was obtained according to the procedure from 3'-trifluoromethylacetophenone (132 mg, 0.7 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 24 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49 (d, J = 6.8 Hz, 3H), 3.68 (s, 3H), 4.44 (q, J = 6.8 Hz, 1H), 6.41-6.45 (m, 2H), 6.67-6.71 (m, 2H), 7.40 (t, J = 7.6 Hz, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.55 (d, J = 7.6 Hz, 1H), 7.63 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.6, 54.6, 56.1, 115.0, 115.2, 123.2 (q, J_{CF} = 3.8 Hz), 124.2 (q, J_{CF} = 3.8 Hz), 124.7 (q, J_{CF} = 270.6 Hz), 129.6, 129.7, 131.3 (q, J_{CF} = 31.6 Hz), 141.6, 147.2, 152.6; HRMS for $C_{16}H_{17}F_3NO$ $[M+H]^+$: *m/z* Calcd: 296.1262; Found: 296.1267; Elemental analysis calcd (%) for $C_{16}H_{16}F_3NO$: C, 65.08; H, 5.46; N, 4.74; Found: C, 65.33; H,

5.55; N, 4.54; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 1.0 mL/min, λ = 254 nm): t_R = 17.2 min (minor), t_R = 25.9 min (major).



4-Methoxy-*N*-[1-(3-nitrophenyl)ethyl]aniline (Table 4-2, entry 15)[8a]

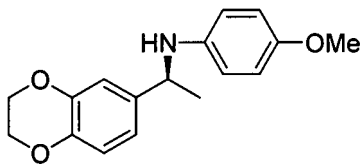
The product (120 mg, 88% yield, 81% ee) was obtained according to the procedure from 3'-nitroacetophenone (116 mg, 0.7 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 24 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.52 (d, J = 6.8 Hz, 3H), 3.68 (s, 3H), 3.86 (brs, 1H), 4.50 (q, J = 6.8 Hz, 1H), 6.41-6.45 (m, 2H), 6.67-6.71 (m, 2H), 7.47 (t, J = 8.0 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 8.07 (ddd, J = 8.0, 2.0, 0.8 Hz, 1H), 8.24 (t, J = 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.5, 54.3, 56.1, 115.0, 115.3, 121.4, 122.5, 130.1, 132.7, 141.2, 148.6, 149.1, 152.7; HRMS for $C_{15}H_{17}N_2O_3$ $[M+H]^+$: *m/z* Calcd: 273.1239; Found: 273.1248; Elemental analysis calcd (%) for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29; Found: C, 65.84; H, 5.87; N, 10.36; HPLC (Chiralcel OD-H, hexane:isopropanol:diethylamine = 90:10:0.1, flow rate 1 mL/min, λ = 254 nm): t_R = 22.7 min (minor), t_R = 30.0 min (major).



4-Methoxy-*N*-[1-(naphthalen-2-yl)ethyl]aniline (Table 4-2, entry 16)[2b,4,7a,8a,15,18,20]

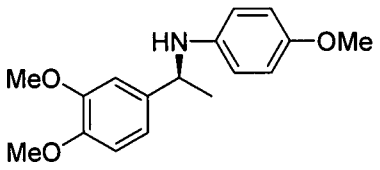
The product (126 mg, 91% yield, 96% ee) was obtained according to the procedure from 2'-acetonaphthone (102 mg, 0.6 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 24 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.57 (d, J = 6.8 Hz, 3H), 3.67 (s, 3H), 4.56 (q, J =

6.8 Hz, 1H), 6.50-6.53 (m, 2H), 6.65-6.69 (m, 2H), 7.40-7.51 (m, 3H), 7.78-7.82 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.5, 55.0, 56.1, 115.2, 124.8, 124.9, 125.9, 126.4, 128.1, 128.2, 128.8, 133.2, 134.0, 141.9, 143.3, 152.4; HRMS for $C_{19}H_{20}NO$ $[M+H]^+$: *m/z* Calcd: 278.1545; Found: 278.1546; Elemental analysis calcd (%) for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05; Found: C, 82.01; H, 6.77; N, 5.21; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): t_R = 38.2 min (minor), t_R = 46.2 min (major).



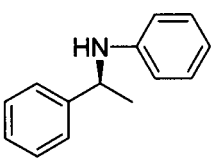
_N_-[1-(2, 3-Dihydro-1,4-benzodioxin-6-yl)ethyl]-4-methoxyaniline (Table 4-2, entry 17)

The product (131 mg, 92% yield, 95% ee) was obtained according to the procedure from 1,4-benzodioxan-6-yl methyl ketone (107 mg, 0.6 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 24 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.43 (d, *J* = 6.8 Hz, 3H), 3.67 (s, 3H), 4.18 (s, 4H), 4.28 (q, *J* = 6.8 Hz, 1H), 6.45-6.48 (m, 2H), 6.67-6.70 (m, 2H), 6.78-6.83 (m, 2H), 6.86 (d, *J* = 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.6, 54.1, 56.2, 64.7, 64.8, 115.0, 115.1, 115.2, 117.7, 119.2, 139.5, 142.1, 142.8, 144.0, 152.3; HRMS for $C_{17}H_{20}NO_3$ $[M+H]^+$: *m/z* Calcd: 286.1443; Found: 286.1437; Elemental analysis calcd (%) for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91; Found: C, 71.73; H, 6.82; N, 4.81; HPLC (Chiralcel OD-H, hexane:isopropanol:diethylamine = 90:10:0.1, flow rate 1.0 mL/min, λ = 254 nm): t_R = 16.0 min (minor), t_R = 19.0 min (major).



***N*-[1-(3, 4-Dimethoxyphenyl)ethyl]-4-methoxyaniline (Table 4-2, entry 18)**[7a,8a]

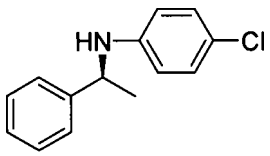
The product (129 mg, 90% yield, 93% ee) was obtained according to the procedure from 3',4'-dimethoxyacetophenone (108 mg, 0.6 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 24 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49 (d, J = 6.8 Hz, 3H), 3.70 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 4.35 (q, J = 6.8 Hz, 1H), 6.48-6.51 (m, 2H), 6.68-6.72 (m, 2H), 6.80-6.82 (m, 1H), 6.88-6.91 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.5, 54.6, 56.1, 56.2, 56.3, 109.5, 111.6, 115.0, 115.1, 118.2, 138.6, 142.1, 148.2, 149.5, 152.4; HRMS for $C_{17}H_{22}NO_3$ $[M+H]^+$: *m/z* Calcd: 288.1600; Found: 288.1594; Elemental analysis calcd (%) for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87; Found: C, 71.23; H, 7.42; N, 4.62; HPLC (Chiralcel OD-H, hexane:isopropanol:diethylamine = 90:10:0.1, flow rate 1.0 mL/min, λ = 254 nm): t_R = 18.8 min (minor), t_R = 21.8 min (major).



***N*-(1-Phenylethyl)aniline (Table 4-3, entry 1)**[2d,4,8a,15,19-21]

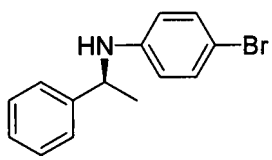
The product (91 mg, 92% yield, 93% ee) was obtained according to the procedure from acetophenone (84 mg, 0.7 mmol) and aniline (47 mg, 0.5 mmol) in 24 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49 (d, J = 6.8 Hz, 3H), 4.01 (brs, 1H), 4.47 (q, J = 6.8 Hz, 1H), 6.48-6.51 (m, 2H), 6.61-6.65 (m, 1H), 7.06-7.10 (m, 2H), 7.18-7.23 (m, 1H), 7.28-7.36 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.5, 53.9, 113.8, 117.7, 126.3, 127.3, 129.1, 129.6, 145.7, 147.8; HRMS for $C_{14}H_{16}N$ $[M+H]^+$: *m/z* Calcd: 198.1283;

Found: 198.1282; Elemental analysis calcd (%) for $C_{14}H_{15}N$: C, 85.24; H, 7.66; N, 7.10; Found: C, 85.26; H, 7.80; N, 6.95; HPLC (Chiralcel OD-H, hexane:isopropanol: = 98:2, flow rate 0.5 mL/min, λ = 254 nm): t_R = 20.6 min (major), t_R = 25.6 min (minor).



4-Chloro-*N*-(1-phenylethyl)aniline (Table 4-3, entry 2)[2d,16,18,21]

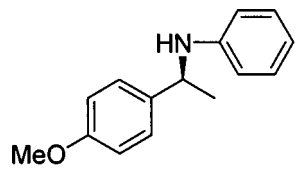
The product (99 mg, 86% yield, 87% ee) was obtained according to the procedure from acetophenone (84 mg, 0.7 mmol) and 4-chloroaniline (64 mg, 0.5 mmol) in 24 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47 (d, J = 6.8 Hz, 3H), 4.04 (brs, 1H), 4.40 (q, J = 6.8 Hz, 1H), 6.37-6.41 (m, 2H), 6.98-7.02 (m, 2H), 7.19-7.24 (m, 1H), 7.27-7.32 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.5, 54.0, 114.9, 122.2, 126.2, 127.5, 129.2, 129.4, 145.2, 146.3; HRMS for $C_{14}H_{15}{}^{35}ClN$ $[M+H]^+$: *m/z* Calcd: 232.0893; Found: 232.0900; Elemental analysis calcd (%) for $C_{14}H_{14}ClN$: C, 72.57; H, 6.09; N, 6.04; Found: C, 72.38; H, 6.18; N, 5.97; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 1.0 mL/min, λ = 254 nm): t_R = 11.6 min (minor), t_R = 14.5 min (major).



4-Bromo-*N*-(1-phenylethyl)aniline (Table 4-3, entry 3)[2d,8a,18]

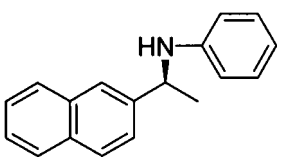
The product (117 mg, 85% yield, 85% ee) was obtained according to the procedure from acetophenone (84 mg, 0.7 mmol) and 4-bromoaniline (86 mg, 0.5 mmol) in 24 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.48 (d, J = 6.8 Hz, 3H), 4.06 (brs, 1H), 4.41 (q, J = 6.8

Hz, 1H), 6.33-6.37 (m, 2H), 7.11-7.15 (m, 2H), 7.18-7.25 (m, 1H), 7.28-7.32 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.4, 53.9, 109.3, 115.4, 126.2, 127.5, 129.2, 132.2, 145.1, 146.6; HRMS for $C_{14}H_{15}{}^{79}BrN$ $[M+H]^+$: *m/z* Calcd: 276.0388; Found: 276.0386; Elemental analysis calcd (%) for $C_{14}H_{14}BrN$: C, 60.89; H, 5.11; N, 5.07; Found: C, 70.02; H, 5.18; N, 5.00; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): t_R = 24.1 min (minor), t_R = 30.2 min (major).



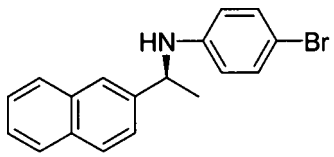
_N_-[1-(4-Methoxyphenyl)ethyl]aniline (Table 4-3, entry 4)[2d,8a,16-19]

The product (104 mg, 92% yield, 91% ee) was obtained according to the procedure from 4'-methoxyacetophenone (105 mg, 0.7 mmol) and aniline (47 mg, 0.5 mmol) in 24 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47 (d, *J* = 6.8 Hz, 3H), 3.75 (s, 3H), 3.93 (brs, 1H), 4.43 (q, *J* = 6.8 Hz, 1H), 6.49 (d, *J* = 8.0 Hz, 2H), 6.63 (t, *J* = 7.6 Hz, 1H), 6.82-6.86 (m, 2H), 7.06-7.10 (m, 2H), 7.25-7.28 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.5, 53.3, 55.7, 113.8, 114.5, 117.6, 127.4, 129.6, 137.7, 147.8, 158.9; HRMS for $C_{15}H_{18}NO$ $[M+H]^+$: *m/z* Calcd: 228.1388; Found: 228.1388; Elemental analysis calcd (%) for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16; Found: C, 78.42; H, 7.50; N, 6.04; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): t_R = 25.3 min (major), t_R = 28.5 min (minor).



_N_-(1-[Naphthalen-2-yl)ethyl]aniline (Table 4-3, entry 5)[8a,15,17,18,20]

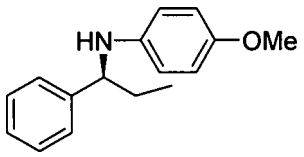
The product (114 mg, 92% yield, 91% ee) was obtained according to the procedure from 2'-acetonaphthone (119 mg, 0.7 mmol) and aniline (47 mg, 0.5 mmol) in 24 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.59 (d, J = 6.8 Hz, 3H), 4.17 (brs, 1H), 4.63 (q, J = 6.8 Hz, 1H), 6.55 (d, J = 8.0 Hz, 2H), 6.63 (t, J = 7.2 Hz, 1H), 7.05-7.10 (m, 2H), 7.41-7.51 (m, 3H), 7.78-7.82 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.4, 54.2, 113.8, 117.8, 124.7, 124.8, 125.9, 126.4, 128.1, 128.3, 128.9, 129.5, 133.2, 134.0, 143.2, 147.7; HRMS for $C_{18}H_{18}N$ $[M+H]^+$: *m/z* Calcd: 248.1439; Found: 248.1449; Elemental analysis calcd (%) for $C_{18}H_{17}N$: C, 87.41; H, 6.93; N, 5.66; Found: C, 87.15; H, 6.89; N, 5.72; HPLC (Chiralcel OD-H, hexane:isopropanol:diethylamine = 90:10:0.1, flow rate 0.5 mL/min, λ = 254 nm): t_R = 19.4 min (major), t_R = 23.0 min (minor).



4-Bromo-*N*-[1-(naphthalen-2-yl]ethyl)aniline (Table 4-3, entry 6)

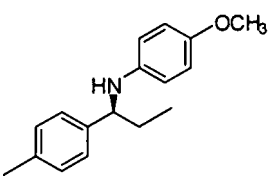
The product (122 mg, 75% yield, 83% ee) was obtained according to the procedure from 2'-acetonaphthone (119 mg, 0.7 mmol) and 4-bromoaniline (86 mg, 0.5 mmol) in 24 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.58 (d, J = 6.8 Hz, 3H), 4.18 (brs, 1H), 4.58 (q, J = 6.8 Hz, 1H), 6.39-6.43 (m, 2H), 7.11-7.15 (m, 2H), 7.42-7.48 (m, 3H), 7.77-7.82 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.4, 54.2, 109.4, 115.4, 124.6, 124.7, 126.1, 126.6, 128.1, 128.2, 129.0, 132.2, 133.2, 133.9, 142.5, 146.6; HRMS for $C_{18}H_{17}{}^{79}BrN$ $[M+H]^+$: *m/z* Calcd: 326.0544; Found: 326.0551; Elemental analysis calcd (%) for $C_{18}H_{16}BrN$: C, 66.27; H, 4.94; N, 4.29; Found: C, 66.13; H, 5.08; N, 4.13; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 1.0 mL/min, λ = 254 nm): t_R =

17.6 min (minor), t_R = 27.7 min (major).



4-Methoxy-*N*-(1-phenylpropyl)aniline (Table 4-4, entry 1)[2b,6d,8a,18,21]

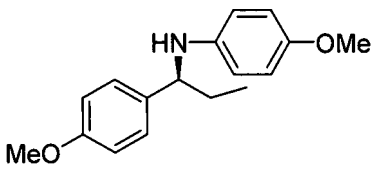
The product (112 mg, 93% yield, 92% ee) was obtained according to the procedure from propiophenone (81 mg, 0.6 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 20 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.94 (t, J = 7.6 Hz, 3H), 1.76-1.87 (m, 2H), 3.68 (s, 3H), 4.14 (t, J = 6.8 Hz, 1H), 6.45-6.48 (m, 2H), 6.66-6.70 (m, 2H), 7.19-7.24 (m, 1H), 7.28-7.34 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.2, 32.1, 56.2, 61.0, 114.9, 115.2, 127.0, 127.3, 128.9, 142.2, 144.5, 152.3; HRMS for $C_{16}H_{20}NO$ $[M+H]^+$: *m/z* Calcd: 242.1545; Found: 242.1542; Elemental analysis calcd (%) for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80; Found: C, 79.77; H, 7.97; N, 5.64; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): t_R = 18.3 min (minor), t_R = 20.5 min (major).



4-Methoxy-*N*-(1-*p*-tolylpropyl)aniline (Table 4-4, entry 2)[8a]

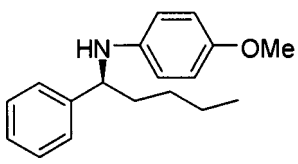
The product (116 mg, 91% yield, 91% ee) was obtained according to the procedure from 4'-methylpropiophenone (89 mg, 0.6 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 20 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.92 (t, J = 7.4 Hz, 3H), 1.74-1.81 (m, 2H), 2.30 (s, 3H), 3.68 (s, 3H), 4.10 (t, J = 6.7 Hz, 1H), 6.44-6.48 (m, 2H), 6.65-6.69 (m, 2H), 7.11 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100

MHz) δ (ppm): 11.2, 21.4, 32.1, 56.1, 60.7, 114.7, 115.1, 126.8, 129.6, 136.7, 141.5, 142.2, 152.1; HRMS for $C_{17}H_{22}NO$ $[M+H]^+$: *m/z* calcd 256.1701, found 256.1702; Elemental analysis calcd (%) for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49; Found: C, 79.99; H, 8.35; N, 5.44; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): t_R = 16.9 min (minor), t_R = 18.7 min (major).



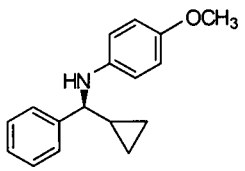
4-Methoxy-*N*-[1-(4-methoxyphenyl)propyl]aniline (Table 4-4, entry 3)

The product (123 mg, 91% yield, 92% ee) was obtained according to the procedure from 4'-methoxypropiophenone (99 mg, 0.6 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 20 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91 (t, *J* = 7.6 Hz, 3H), 1.72-1.88 (m, 2H), 3.68 (s, 3H), 3.77 (s, 3H), 4.09 (t, *J* = 6.8 Hz, 1H), 6.48-6.52 (m, 2H), 6.66-6.70 (m, 2H), 6.82-6.86 (m, 2H), 7.22-7.26 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.2, 31.9, 55.6, 56.1, 60.9, 114.3, 115.1, 115.4, 128.1, 136.1, 141.6, 152.5, 158.9; HRMS for $C_{17}H_{22}NO_2$ $[M+H]^+$: *m/z* Calcd: 272.1651; Found: 272.1642; Elemental analysis calcd (%) for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16; Found: C, 75.33; H, 7.86; N, 5.02; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, = 254 nm): t_R = 13.3 min (minor), t_R = 14.9 min (major).



4-Methoxy-*N*-(phenylpentyl)aniline (Table 4-4, entry 5)[6d,24]

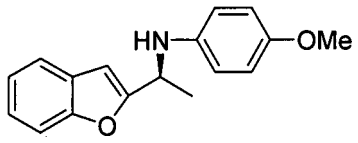
The product (67 mg, 50% yield, 75% ee) was obtained according to the procedure from valerophenone (97 mg, 0.6 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 24 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.14 (t, J = 7.4 Hz, 3H), 1.54-1.64(m, 4H), 1.97-2.06 (m, 2H), 3.91 (s, 3H), 3.93 (br, 1H), 4.47 (t, J = 6.8 Hz, 1H), 6.69-6.74(m, 2H), 6.91-6.95 (m, 2H), 7.43-7.48 (m, 1H), 7.52-7.60 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 22.7, 28.8, 38.8, 55.7, 59.3, 114.5, 114.8, 126.5, 126.8, 128.5, 142.0, 144.7, 152.0 HRMS for $C_{18}H_{24}NO$ $[M+H]^+$: *m/z* Calcd: 270.1858; Found: 270.1851; Elemental analysis calcd (%) for $C_{18}H_{23}NO$: C, 80.26; H, 8.61; N, 5.20; Found: C, 80.42; H, 8.77; N, 5.01; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): t_R = 17.0 min (minor), t_R = 18.4 min (major).



_N_-[Cyclopropyl(phenyl)methyl]-4-methoxyaniline (Table 4-4, entry 6)[8a]

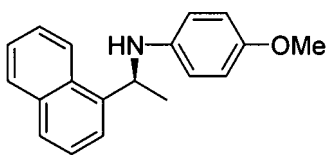
The product (25 mg, 20% yield, 97% ee) was obtained according to the procedure from cyclopropyl phenyl ketone (88 mg, 0.6 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 24 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.28-0.53 (m, 4H), 1.06-1.10 (m, 1H), 3.48 (d, J = 8.4 Hz, 1H), 3.58 (s, 3H), 4.02 (brs, 1H), 6.31-6.56 (m, 2H), 6.56-6.60 (m, 2H), 7.11-7.16 (m, 1H), 7.20-7.24 (m, 2H), 7.29-7.32 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 3.9, 4.7, 20.3, 56.2, 64.3, 115.1, 115.2, 127.0, 127.5, 129.0, 142.4, 144.1, 152.4; HRMS for $C_{17}H_{20}NO$ $[M+H]^+$: *m/z* calcd 254.1545, found 254.1546; Elemental analysis calcd (%) for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53; Found: C, 80.42; H, 7.62; N, 5.43; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min,

λ = 254 nm): t_R = 21.8 min (minor), t_R = 25.8 min (major).



_N_-[1-(benzofuran-2-yl)ethyl]-4-methoxyaniline (Table 4-4, entry 7)

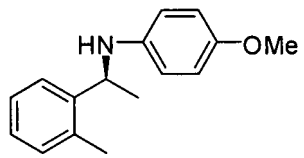
The product (124 mg, 93% yield, 91% ee) was obtained according to the procedure from the 2-benzofuranyl methyl ketone (96 mg, 0.6 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 24 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.59 (d, J = 6.8 Hz, 3H), 3.68 (s, 3H), 4.63 (q, J = 6.8 Hz, 1H), 6.49 (s, 1H), 6.58-6.62 (m, 2H), 6.71-6.75 (m, 2H), 7.14-7.23 (m, 2H), 7.41-7.46 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6, 49.2, 56.1, 102.6, 111.5, 115.3, 115.6, 121.3, 123.1, 124.1, 128.9, 141.4, 153.0, 155.2, 160.9; HRMS for $C_{17}H_{18}NO_2$ $[M+H]^+$: *m/z* Calcd: 268.1338; Found: 268.1330; Elemental analysis calcd (%) for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24; Found: C, 76.44; H, 6.56; N, 5.12; HPLC (Chiralcel OD-H, hexane:isopropanol:diethylamine = 90:10:0.1, flow rate 1.0 mL/min, λ = 254 nm): t_R = 9.6 min (minor), t_R = 10.8 min (major).



4-Methoxy-_N_-[1-(naphthalen-1-yl)ethyl]aniline (Table 4-4, entry 8)[2b]

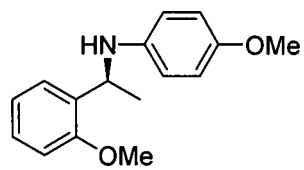
The product (125 mg, 90% yield, 87% ee) was obtained according to the procedure from 1'-acetonaphthone (102 mg, 0.6 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 24 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.61 (d, J = 6.8 Hz, 3H), 3.63 (s, 3H), 3.99 (brs, 1H), 5.19 (q, J = 6.8 Hz, 1H), 6.40-6.43 (m, 2H), 6.61-6.64 (m, 2H), 7.38 (t, J = 7.6 Hz, 1H), 7.47-7.55 (m, 2H); 7.63 (d, J = 6.8 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 8.0

Hz, 1H), 8.14 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.2, 50.6, 56.2, 114.8, 115.3, 122.8, 123.1, 125.9, 126.4, 126.5, 127.8, 129.6, 131.2, 134.6, 140.6, 141.8, 152.4; HRMS for $C_{19}H_{20}NO$ $[M+H]^+$: *m/z* Calcd: 278.1545; Found: 278.1546; Elemental analysis calcd (%) for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05; Found: C, 82.38; H, 6.78; N, 5.14; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 1.0 mL/min, λ = 254 nm): t_R = 17.9 min (minor), t_R = 27.0 min (major).



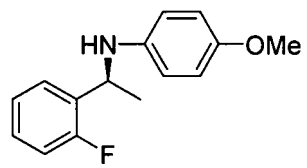
4-Methoxy-*N*-(1-o-tolylethyl)aniline (Table 4-4, entry 9)[2b,6d,7a,20]

The product (111 mg, 92% yield, 91% ee) was obtained according to the procedure from 2'-methylacetophenone (81 mg, 0.6 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 20 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.44 (d, J = 6.8 Hz, 3H), 2.42 (s, 3H), 3.67 (s, 3H), 4.59 (q, J = 6.8 Hz, 1H), 6.38-6.41 (m, 2H), 6.66-6.69 (m, 2H), 7.11-7.16 (m, 3H), 7.40-7.42 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.4, 23.5, 50.9, 56.2, 114.7, 115.3, 125.1, 127.0, 127.1, 131.0, 135.0, 142.0, 143.4, 152.3; HRMS for $C_{16}H_{20}NO$ $[M+H]^+$: *m/z* Calcd: 242.1545; Found: 242.1546; Elemental analysis calcd (%) for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80; Found: C, 79.78; H, 7.99; N, 5.66; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 1.0 mL/min, λ = 254 nm): t_R = 9.1 min (minor), t_R = 11.8 min (major).



4-Methoxy-*N*-[1-(2-methoxyphenyl)ethyl]aniline (Table 4-4, entry 10)[2b,7a]

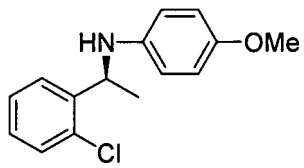
The product (120 mg, 93% yield, 86% ee) was obtained according to the procedure from 2'-methoxyacetophenone (90 mg, 0.6 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 20 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45 (d, J = 6.4 Hz, 3H), 3.67 (s, 3H), 3.87 (s, 3H), 4.76 (q, J = 6.4 Hz, 1H), 6.46-6.49 (m, 2H), 6.65-6.69 (m, 2H), 6.86-6.89 (m, 2H), 7.16-7.23 (m, 1H), 7.29-7.31 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.2, 49.5, 55.7, 56.1, 110.9, 115.1, 115.2, 121.2, 126.9, 128.1, 133.3, 142.0, 152.3, 157.2; HRMS for $C_{16}H_{20}NO_2$ $[M+H]^+$: *m/z* Calcd: 258.1494; Found: 258.1490; Elemental analysis calcd (%) for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44; Found: C, 74.82; H, 7.56; N, 5.40; HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): t_R = 20.2 min (minor), t_R = 24.9 min (major).



_N_-[1-(2-Fluorophenyl)ethyl]-4-methoxyaniline (Table 4-4, entry 11)[4,7a,20]

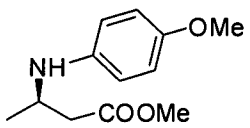
The product (113 mg, 92% yield, 96% ee) was obtained according to the procedure from 2'-fluoroacetophenone (83 mg, 0.6 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 20 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.50 (d, J = 6.8 Hz, 3H), 3.67 (s, 3H), 4.73 (q, J = 6.8 Hz, 1H), 6.45-6.49 (m, 2H), 6.66-6.70 (m, 2H), 6.99-7.05 (m, 2H), 7.14-7.19 (m, 1H), 7.32-7.37 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.8, 48.7, 56.1, 114.9, 115.2, 115.9 (d, J_{CF} = 11.7 Hz), 124.8 (d, J_{CF} = 3.0 Hz), 127.7 (d, J_{CF} = 4.5 Hz), 128.7 (d, J_{CF} = 8.3 Hz), 132.4 (d, J_{CF} = 12.9 Hz), 141.6, 152.5, 160.9 (d, J_{CF} = 243.1 Hz); HRMS for $C_{15}H_{17}FNO$ $[M+H]^+$: *m/z* Calcd: 246.1294; Found: 246.1298; Elemental analysis calcd (%) for $C_{15}H_{16}FNO$: C, 73.45; H, 6.57; N, 5.71; Found: C, 73.34; H, 6.52; N, 5.82;

HPLC (Chiralcel OD-H, hexane:isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): t_R = 18.5 min (minor), t_R = 21.7 min (major).



_N_-[1-(2-Chlorophenyl)ethyl]-4-methoxyaniline (Table 4-4, entry 12)[22]

The product (120 mg, 92% yield, 83% ee) was obtained according to the procedure from 2'-chloroacetophenone (93 mg, 0.6 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 20 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.38 (d, *J* = 6.8 Hz, 3H), 3.58 (s, 3H), 3.78 (brs, 1H), 4.74 (q, *J* = 6.8 Hz, 1H), 6.29-6.33 (m, 2H), 6.57-6.61 (m, 2H), 7.02-7.10 (m, 2H), 7.25-7.27 (m, 1H), 7.35 (dd, *J* = 7.8, 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.5, 51.3, 56.1, 114.7, 115.3, 127.3, 127.8, 128.4, 130.1, 133.0, 141.5, 142.7, 152.4; HRMS for $C_{15}H_{17}{}^{35}ClNO$ $[M+H]^+$: *m/z* Calcd: 262.0999; Found: 262.0997; Elemental analysis calcd (%) for $C_{15}H_{16}ClNO$: C, 68.83; H, 6.16; N, 5.35; Found: C, 68.95; H, 5.99; N, 5.42; HPLC (Chiralcel OD-H, hexane : isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): t_R = 18.6 min (minor), t_R = 21.9 min (major).



3-[(4-methoxyphenyl)amino]butanoate (Table 4-6, entry 13)

The product (98 mg, 88% yield, 80% ee) was obtained according to the procedure from methyl acetoacetate (70 mg, 0.6 mmol) and *p*-anisidine (62 mg, 0.5 mmol) in 24 h; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25 (d, *J* = 6.4 Hz, 3H), 2.41 (dd, *J* = 6.8, 15.2 Hz, 1H), 2.62 (dd, *J* = 5.2, 15.2 Hz, 1H), 3.67 (s, 3H), 3.74 (s, 3H), 3.81-3.89 (m, 1H), 6.60-6.64

(m, 2H), 6.76-6.80 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.0, 41.1, 47.7, 52.0, 56.1, 115.3, 115.9, 141.1, 152.9, 172.8; MS CI m/z (%): 224.1 $[M + H]^+$; Elemental analysis calcd (%) for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27; Found: C, 64.65; H, 7.99; N, 6.42; HPLC (Chiralcel OD-H, hexane : isopropanol = 98:2, flow rate 0.5 mL/min, λ = 254 nm): t_R = 41.5 min (major), t_R = 44.1 min (minor).

5 References

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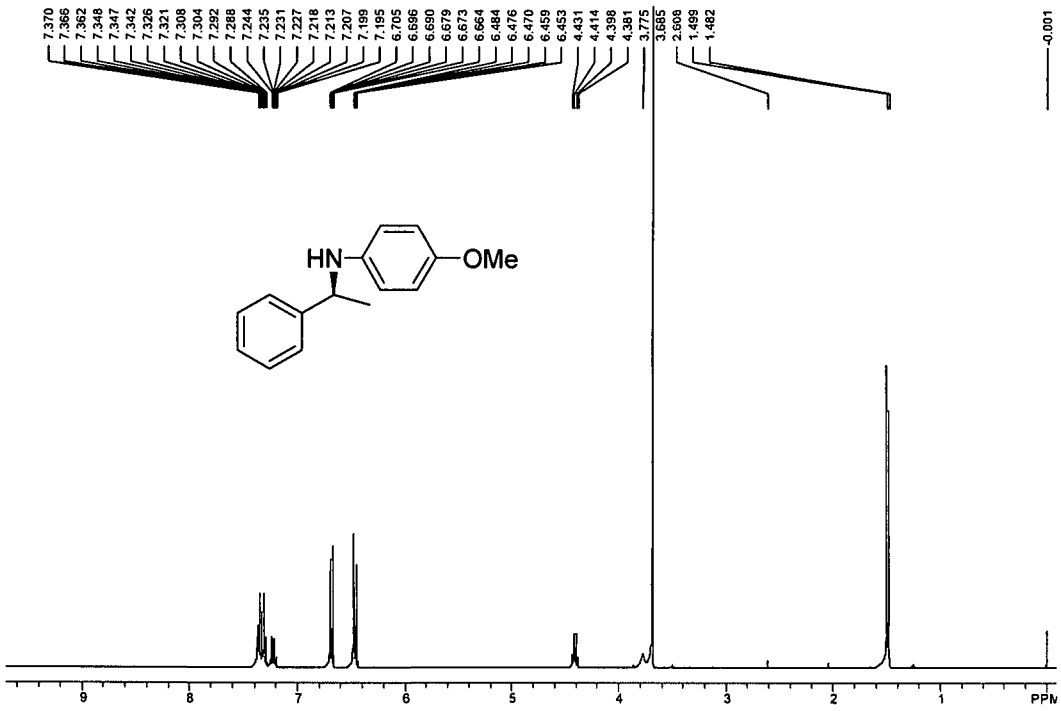
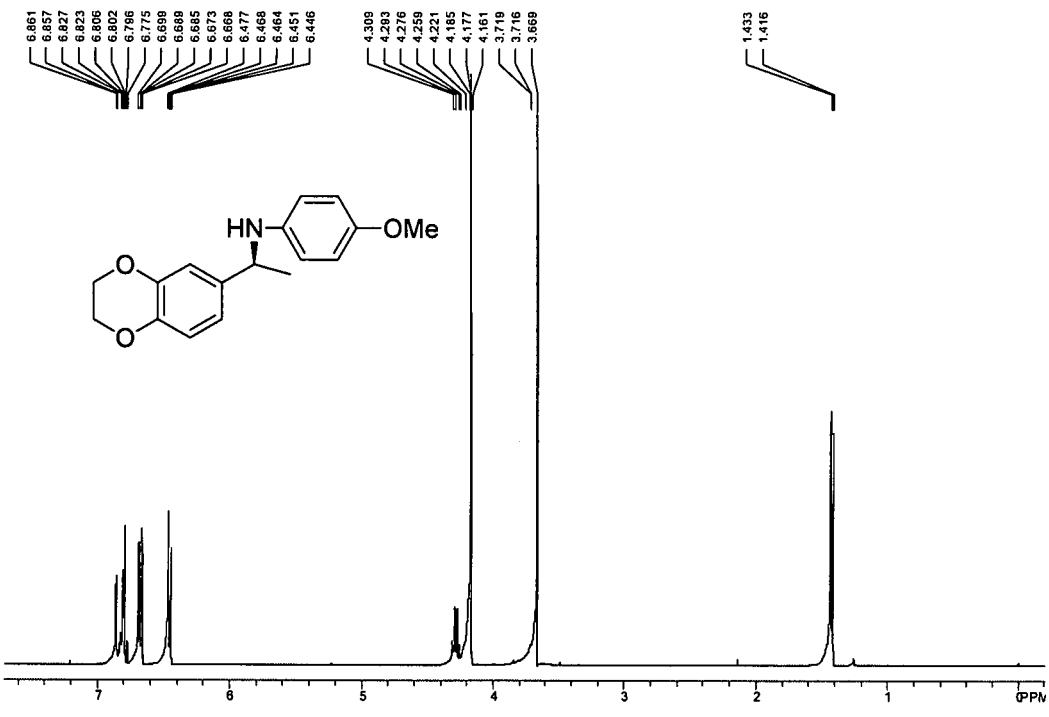
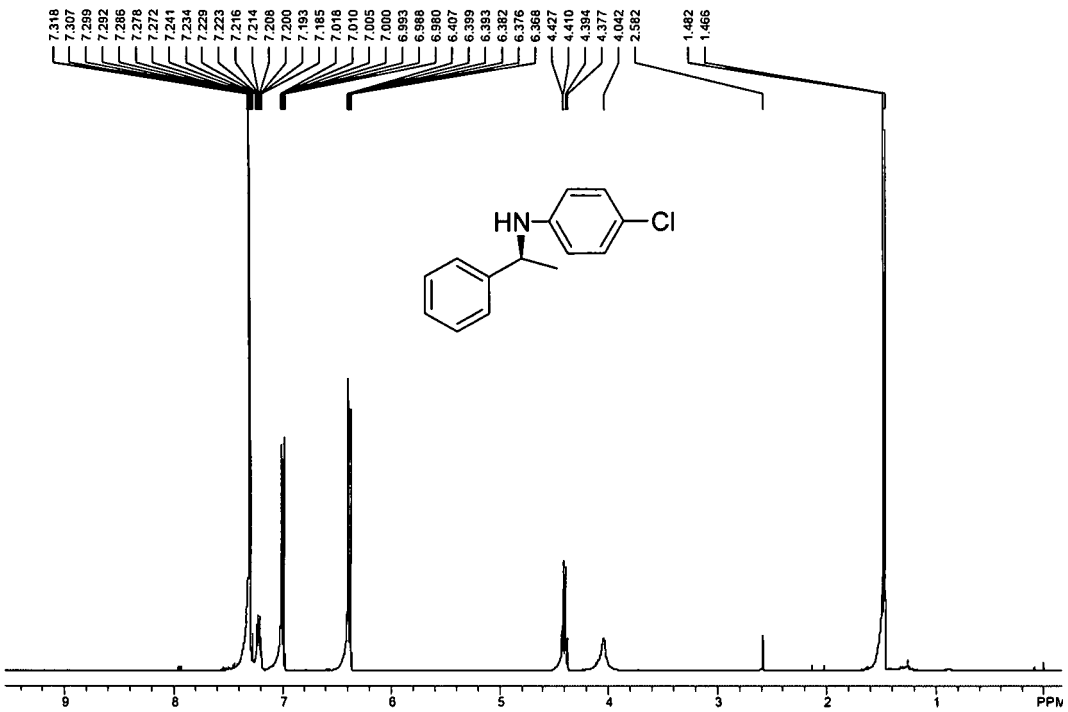
6. ^{1}H NMR Spectra (400 MHz, $CDCl_3$)



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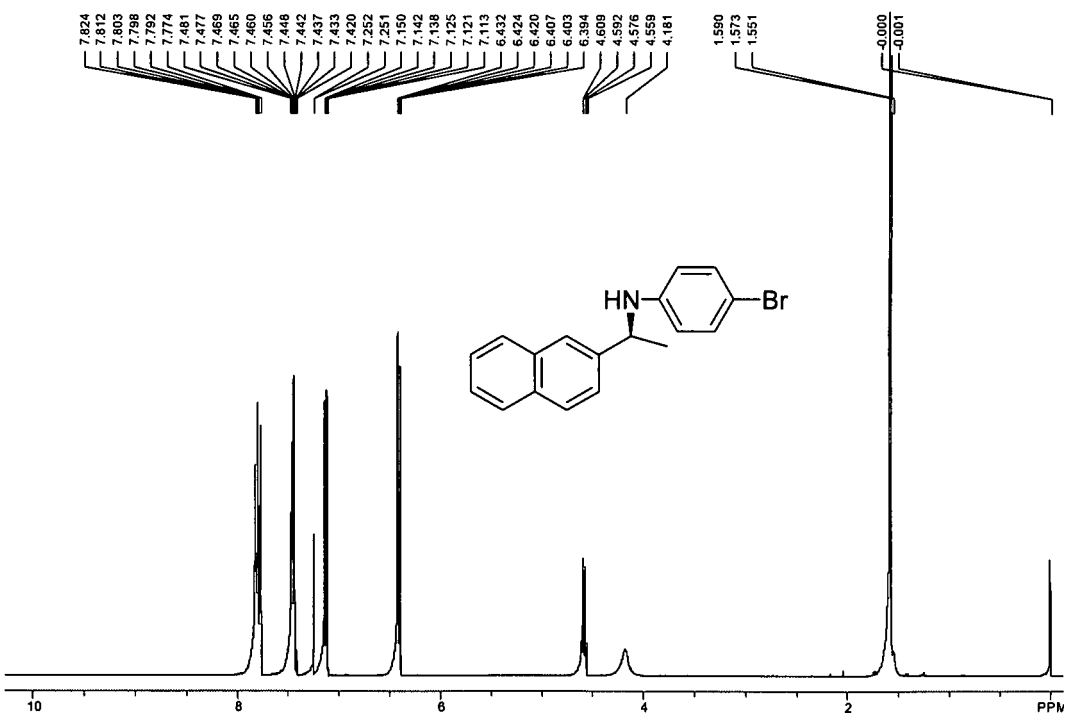
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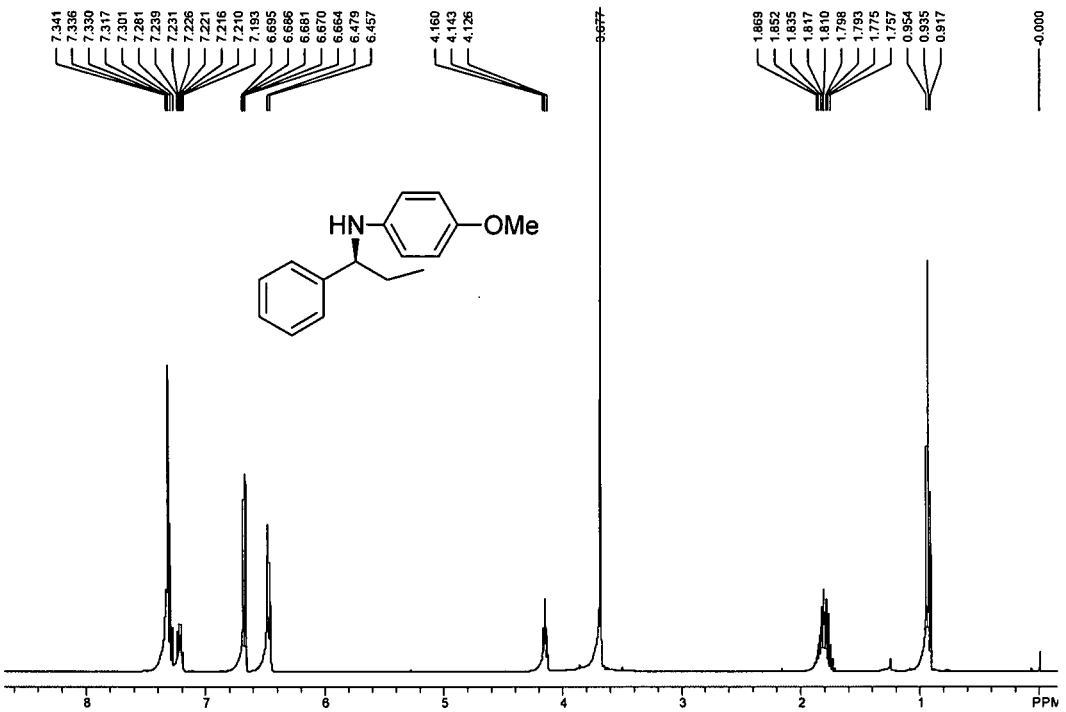
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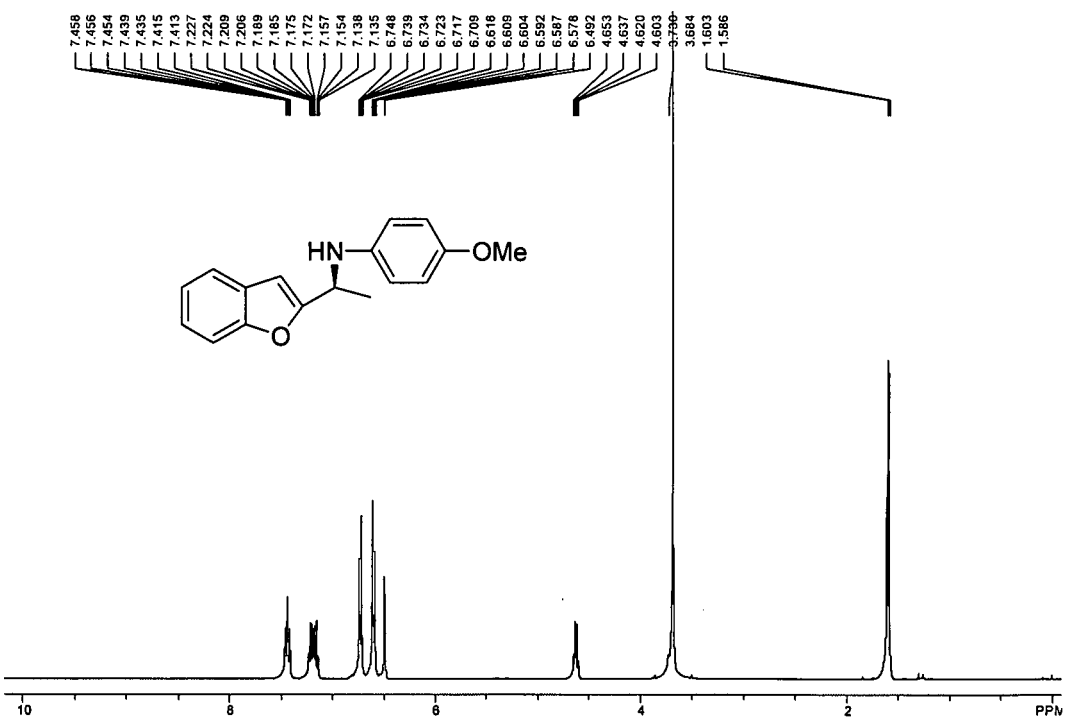
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